

**AGGRENEX<sup>®</sup> Capsules**  
**(aspirin/extended-release dipyridamole)**

**ACADEMY OF MANAGED CARE PHARMACY (AMCP)**  
**FORMULARY DOSSIER**

**BOEHRINGER INGELHEIM PHARMACEUTICALS, INC.**

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## **1 ££££ INTRODUCTION**

The purpose of this formulary submission dossier is to present the clinical and economic rationale to support the acceptance and use of Aggrenox<sup>®</sup> (aspirin/extended-release dipyridamole) in the reduction of the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis. Aggrenox<sup>®</sup> is a combination anti-platelet agent that is prescribed orally twice daily. This dossier presents the ways in which Aggrenox<sup>®</sup> will add value to the current management of stroke, both in terms of clinical effectiveness and economic efficiency.

Section 2 provides a description of Aggrenox<sup>®</sup> (including a cross-label comparison with its main competitors (aspirin, Plavix<sup>®</sup>, Ticlid<sup>®</sup>), secondary stroke, and its management.

Section 3 provides a summary of the supporting clinical and pharmacoeconomic evidence for Aggrenox<sup>®</sup> based on results from pivotal efficacy studies.

Section 4 provides a brief overview of the cost-effectiveness of Aggrenox<sup>®</sup>.

Section 5 provides a summary of the clinical and economic value of Aggrenox<sup>®</sup>.



**Table 1. Cross-label comparisons for products in same therapeutic class**

	<b>AGGRENOX® (aspirin/extended release dipyridamole)</b>	<b>ASPIRIN (acetylsalicylic acid)</b>
<b>Chemical formula</b>	<b>Dipyridamole:</b> 2,6- bis(diethanolamino)-4,8-dipiperidino-pyrimido (5,4-d) pyrimidine <b>Aspirin:</b> benzoic acid, 2-(acetyloxy)-	2-(acetyloxy) benzoic acid
<b>Empirical formula</b>	<b>Dipyridamole:</b> C <sub>24</sub> H <sub>40</sub> N <sub>8</sub> O <sub>4</sub> <b>Aspirin:</b> C <sub>9</sub> H <sub>8</sub> O <sub>4</sub>	C <sub>9</sub> H <sub>8</sub> O <sub>4</sub>
<b>Molecular weight</b>	<b>Dipyridamole:</b> 504.63 <b>Aspirin:</b> 180.16	180.16
<b>Available formulations and indicated strengths</b>	Each capsule contains 25mg aspirin, as an immediate-release, sugar coated tablet and 200 mg extended-release dipyridamole pellets. The recommended dose is one capsule given orally twice daily, one in the morning and one in the evening.	<ul style="list-style-type: none"> <li>• <b>Ischemic Stroke and TIA:</b> 50-325 mg once a day. Continue therapy indefinitely.</li> <li>• <b>Suspected Acute Myocardial Infarction (MI):</b> Initiate therapy with 160-162.5 mg as soon as MI is suspected. Maintain with 160-162.5 mg daily for 30 days post-infarction. After 30 days, consider further therapy based on dosage and administration for prevention of recurrent MI.</li> <li>• <b>Prevention of Recurrent MI:</b> 75-325 mg once a day. Continue therapy indefinitely.</li> <li>• <b>Unstable Angina Pectoris:</b> 75-325 mg once a day. Continue therapy indefinitely.</li> <li>• <b>Chronic Stable Angina Pectoris:</b> 75-325 mg once a day. Continue therapy indefinitely.</li> <li>• <b>Coronary Artery Bypass Grafts (CABG):</b> 325 mg daily starting 6 hours post-procedure. Continue therapy for 1 year post-procedure.</li> <li>• <b>Percutaneous Transluminal Coronary Angioplasty (PTCA):</b> Initiate therapy with 325 mg 2 hours prior to surgery. Maintain with 160-325 mg daily. Continue therapy indefinitely.</li> <li>• <b>Carotid Endarterectomy (CE):</b> Initiate therapy prior to surgery with 80-650 mg once or twice daily. Continue therapy indefinitely.</li> <li>• <b>Rheumatoid Arthritis (RA):</b> Initiate therapy with 3 g daily in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 g/mL.</li> <li>• <b>Juvenile Rheumatoid Arthritis (JRA):</b> Initiate therapy with 90-130 mg/kg/day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 g/mL.</li> <li>• <b>Spondyloarthropathies:</b> Up to 4 g per day in divided doses.</li> <li>• <b>Osteoarthritis (OA):</b> Up to 3 g per day in divided doses.</li> <li>• <b>Arthritis and Pleurisy of Systemic Lupus Erythematosus (SLE):</b> Initiate therapy with 3 g per day in divided doses. Increase as needed for anti-inflammatory efficacy with target plasma salicylate levels of 150-300 g/mL.</li> </ul>
<b>Indications</b>	To reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis	<b>Vascular Indications:</b> Aspirin is indicated <ul style="list-style-type: none"> <li>• To reduce the combined risk of death and nonfatal stroke in patients who have had ischemic stroke or transient ischemia of the brain due to fibrin emboli.</li> <li>• To reduce the risk of vascular mortality in patients with a suspected acute MI.</li> <li>• To reduce the combined risk of death and nonfatal MI in patients with a previous MI or unstable angina pectoris.</li> <li>• To reduce the combined risk of MI and sudden death in patients with chronic stable</li> </ul>

	<b>AGGRENOX® (aspirin/extended release dipyridamole)</b>	<b>ASPIRIN (acetylsalicylic acid)</b>
		<p>angina pectoris.</p> <p><b>Revascularization Procedures:</b> Aspirin is indicated in patients who have undergone CABG, PCTA or CE when a pre-existing condition for aspirin therapy is present.</p> <p><b>Rheumatologic Diseases:</b> Aspirin is indicated for relief of the signs and symptoms of RA, JRA, OA, spondyloarthropathies, and arthritis and pleurisy associated with SLE.</p>
<b>Clinical Pharmacology</b>		
Mechanism of action	<p>The antithrombotic action of Aggrenox is the result of additive antiplatelet effects of dipyridamole and aspirin.</p> <p><b>Dipyridamole:</b> reduces platelet aggregation through two main mechanisms.</p> <ul style="list-style-type: none"> <li>It inhibits adenosine uptake into platelets, endothelial cells, and erythrocytes in a dose-dependent manner at therapeutic concentrations (0.5-1.9µg/mL). This results in increased local concentrations of adenosine that act on the platelet A<sub>2</sub> receptor to stimulate platelet adenylyl cyclase, increasing cyclic-3',5'-adenosine monophosphate (cAMP) levels in response to platelet activating factor (PAF), collagen, and adenosine diphosphate (ADP).</li> <li>It also inhibits phosphodiesterase (PDE) in various tissues thereby augmenting the increase in cyclic-3',5'-guanosine-monophosphate (cGMP) produced by endothelium-derived relaxing factor (ERDF).</li> </ul> <p><b>Aspirin:</b> inhibits platelet aggregation by irreversible inhibition of platelet cyclo-oxygenase and thus inhibits generation of thromboxane A<sub>2</sub>, a powerful inducer of platelet aggregation and vasoconstriction.</p>	<ul style="list-style-type: none"> <li>Aspirin inhibits platelet aggregation by irreversibly inhibiting platelet cyclo-oxygenase (for the life of the platelet) and thus inhibits generation of thromboxane A<sub>2</sub>, a powerful inducer of platelet aggregation and vasoconstriction.</li> <li>At somewhat higher doses, aspirin reversibly inhibits the formation of prostaglandin I<sub>2</sub> (prostacyclin), which is an arterial vasodilator and inhibits platelet aggregation.</li> <li>At higher doses aspirin is also an effective anti-inflammatory agent, due to inhibition of inflammatory mediators via non-specific suppression of cyclo-oxygenase activity in peripheral tissues.</li> </ul>
<b>Pharmacokinetics</b>		
Absorption	<p><b>Dipyridamole:</b> Peak plasma levels are achieved 2 hours (range 1–6 hours) after administration of a daily dose of 400 mg extended-release dipyridamole ( 200 mg b.i.d.) . At steady-state, peak plasma concentration is 1.98µg/mL (1.01-3.99µg/mL) and the steady-state trough concentrations is 0.53µg/mL (0.18-1.01µg/mL).</p> <p><b>Aspirin:</b> Peak plasma levels of aspirin are achieved 0.63 hours (0.5–1 hour) after administration of a daily dose of 50 mg aspirin (25 mg bid). Peak plasma concentration at steady-state is 319 ng/mL (175-463 ng/mL).</p>	<p>Following absorption, aspirin is hydrolyzed to salicylic acid with peak levels of salicylic acid occurring within 1 hour of dosing. The rate of absorption from the GI tract is dependent upon the dosage form, the presence or absence of food, gastric pH, and other physiologic factors. Enteric coated aspirin products are erratically absorbed from the GI tract.</p>
Food Effects	<p><b>Dipyridamole:</b> Peak plasma levels (C<sub>max</sub>) and total absorption (AUC) decreased at steady-state by 20-30% when Aggrenox was taken with a high-fat meal compared with fasting . Food effect is not considered clinically relevant due to the similar degree of inhibition of adenosine uptake at these plasma concentrations.</p> <p><b>Aspirin:</b> No difference for aspirin in AUC at steady-state was observed when Aggrenox was taken with a high-fat meal compared with fasting. The approximately 50% decrease in C<sub>max</sub> was not considered clinically relevant based on a similar degree of cyclooxygenase inhibition comparing the fed and fasted states.</p>	No data is available
Metabolism	<p><b>Dipyridamole:</b> Dipyridamole is metabolized in the liver by conjugation with glucuronic acid, of which monoglucuronide (low pharmacodynamic activity) is the primary metabolite. In plasma, about 80% of the total amount is present as parent compound and 20% as monoglucuronide.</p>	<p>Aspirin is rapidly hydrolyzed in the plasma to salicylic acid. Plasma concentrations of aspirin are always low and rarely exceed 20 µg/mL at ordinary therapeutic doses; levels are essentially undetectable 1-2 hours after dosing.</p>

	<b>AGGRENOX® (aspirin/extended release dipyridamole)</b>	<b>ASPIRIN (acetylsalicylic acid)</b>
	<p><b>Aspirin:</b> Aspirin undergoes moderate hydrolysis to salicylic acid in the liver and the gastrointestinal wall, with 50%–75% of an administered dose reaching the systemic circulation as intact aspirin. Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites.</p>	<p>Salicylic acid is primarily conjugated in the liver to form salicyluric acid, a phenolic glucuronide, an acyl glucuronide, and a number of minor metabolites.</p>
Half-life	<p><b>Dipyridamole:</b> With intravenous treatment of dipyridamole, a triphasic profile is obtained. Due to the extended release oral formulation, only one phase (terminal) is apparent. The half-life for this phase is 13.6 hours.</p> <p><b>Aspirin:</b> Aspirin is rapidly hydrolyzed in plasma to salicylic acid, with a half-life of 20 minutes. The half-life of salicylic acid is 1.71 hours. At higher doses, elimination of salicylic acid has a half-life of 6 hours or higher.</p>	<p>The plasma half-life of aspirin is approximately 15 minutes. As the dose of aspirin increases; the plasma half-life of salicylate lengthens. Doses 300-650 mg have a half-life of 3.1 to 3.2 hours. With doses of 1 gram, the half-life is increased to 5 hours and with 2 grams it is increased to about 9 hours.</p>
Volume of distribution	<p><b>Dipyridamole:</b> Dipyridamole is highly lipophilic, but it has been shown that it does not cross the blood-brain barrier to any significant extent in animals. The steady-state volume of distribution of dipyridamole is about 92 L. Approximately 99% of dipyridamole is bound to plasma proteins, predominantly to alpha 1-acid glycoprotein and albumin.</p> <p><b>Aspirin:</b> Aspirin is poorly bound to plasma proteins and its apparent volume of distribution is low (10 L). Salicylic acid is highly bound to plasma proteins, but its binding is concentration-dependent. At low concentrations (&lt;100 mg/mL), ~ 90% of salicylic acid is bound to albumin. Salicylic acid is widely distributed to all tissues and fluids in the body, including the central nervous system, breast milk, and fetal tissues.</p>	<p>Salicylic acid is widely distributed to all tissues and fluids in the body including the central nervous system, breast milk, and fetal tissues. The highest concentrations are found in the plasma, liver, renal cortex, heart, and lungs.</p> <p>The protein binding of salicylate is concentration dependent. At low concentrations (&lt;100 µg/mL), ~ 90% of salicylic acid is bound to albumin, while at higher concentrations (&gt;400 µg/mL), only ~ 75% is bound.</p>
Excretion	<p><b>Dipyridamole:</b> About 95% of the glucuronide metabolite is excreted via bile into the feces, with some evidence of enterohepatic circulation. Renal excretion of parent compound is negligible and urinary excretion of the glucuronide metabolite is low (about 5%).</p> <p><b>Aspirin:</b> Renal excretion of unchanged drug depends upon urinary pH. As urinary pH rises above 6.5, the renal clearance of free salicylate increases from &lt;5% to &gt;80%. Following therapeutic doses, about 10% is excreted as salicylic acid, 75% as salicyluric acid, and the remainder as the phenolic and acyl glucuronides, in urine.</p>	<p>Salicylates are excreted primarily by the kidney. Studies in man indicate that salicylate is excreted in the urine as free salicylic acid (10%), salicyluric acid (75%), salicylic phenolic (10%) and acyl (5%) glucuronides and gentisic acid (&lt;1%).</p>
Special populations	<ul style="list-style-type: none"> <li>• <i>Geriatric Patients:</i> Plasma concentrations of dipyridamole in healthy elderly subjects (&gt;65 years) were about 40% higher than in subjects &lt;55 years receiving treatment with Aggrenox.</li> <li>• <i>Pediatric patients:</i> Safety and effectiveness of Aggrenox have not been studied in pediatric patients. Due to the aspirin component, use of this product in the pediatric population is not recommended.</li> <li>• <i>Hepatic Dysfunction:</i> No studies have been conducted with the Aggrenox formulation in patients with hepatic dysfunction. In a study conducted with an intravenous formulation of dipyridamole, patients with mild to severe hepatic insufficiency showed no change in plasma concentrations of dipyridamole but showed an increase in pharmacologically inactive monoglucuronide metabolite. Dipyridamole can be dosed without restriction as long as there is no evidence of hepatic failure. Aspirin should be avoided in patients with severe hepatic insufficiency.</li> <li>• <i>Renal Dysfunction:</i> No studies have been conducted with the Aggrenox formulation in patients with renal dysfunction. However, no changes were observed in patients with a creatinine clearance ≤15 mL/min (renal impairment) to &gt;100 mL/min (normal renal function) in ESPS2. Aspirin should be avoided in patients with severe renal failure</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Geriatric patients:</i> No dose adjustments are necessary.</li> <li>• <i>Pediatric patients:</i> Patients &lt; 12 years of age should not be treated with aspirin unless prescribed by a physician.</li> <li>• <i>Hepatic Dysfunction:</i> Aspirin is to be avoided in patients with severe hepatic insufficiency.</li> <li>• <i>Renal Dysfunction:</i> Aspirin is to be avoided in patients with severe renal failure glomerular filtration rate &lt; 10 mL/min).</li> </ul>

	<b>AGGRENOX® (aspirin/extended release dipyridamole)</b>	<b>ASPIRIN (acetylsalicylic acid)</b>
	(glomerular filtration rate <10mL/min).	
<b>Contraindications</b>	<p>Aggrenox is contraindicated in patients with hypersensitivity to dipyridamole, aspirin or any other product components. Because of the aspirin component, Aggrenox is also contraindicated in the following situations:</p> <ul style="list-style-type: none"> <li>• <i>Allergy</i>: Aspirin is contraindicated in patients with known allergy to nonsteroidal anti-inflammatory drugs (NSAIDs) and in patients with the syndrome of asthma, rhinitis, and nasal polyps. Aspirin may cause severe urticaria, angioedema or bronchospasm (asthma).</li> <li>• <i>Reye's Syndrome</i>: Aspirin should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of aspirin in certain viral illnesses.</li> </ul>	<p>Aspirin is contraindicated in patients with:</p> <ul style="list-style-type: none"> <li>• <i>Allergy</i>: Aspirin is contraindicated in patients with known allergy to (NSAIDs) and in patients with the syndrome of asthma, rhinitis, and nasal polyps. Aspirin may cause severe urticaria, angioedema or bronchospasm (asthma).</li> <li>• <i>Reye's Syndrome</i>: Aspirin should not be used in children or teenagers for viral infections, with or without fever, because of the risk of Reye's syndrome with concomitant use of aspirin in certain viral illnesses.</li> </ul>
<b>Warnings</b>	<ul style="list-style-type: none"> <li>• <i>Alcohol</i>: Patients who consume three or more alcoholic drinks every day should be counseled about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin.</li> <li>• <i>Coagulation abnormalities</i>: Even low doses of aspirin can inhibit platelet function leading to an increase in bleeding time. This can adversely affect patients with inherited or acquired (liver disease or vitamin K deficiency) bleeding disorders.</li> <li>• <i>GI side effects</i>: GI side effects include stomach pain, heartburn, nausea, vomiting, and gross GI bleeding. Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms.</li> <li>• <i>Peptic ulcer disease</i>: Patients with a history of active peptic ulcer disease should avoid using aspirin, which can cause gastric mucosal irritation, and bleeding.</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Alcohol</i>: Patients who consume three or more alcoholic drinks every day should be counseled about the bleeding risks involved with chronic, heavy alcohol use while taking aspirin.</li> <li>• <i>Coagulation abnormalities</i>: Even low doses of aspirin can inhibit platelet function leading to an increase in bleeding time. This can adversely affect patients with inherited or acquired (liver disease or vitamin K deficiency) bleeding disorders.</li> <li>• <i>GI side effects</i>: GI side effects include stomach pain, heartburn, nausea, vomiting, and gross GI bleeding. Although minor upper GI symptoms, such as dyspepsia, are common and can occur anytime during therapy, physicians should remain alert for signs of ulceration and bleeding, even in the absence of previous GI symptoms.</li> <li>• <i>Peptic ulcer disease</i>: Patients with a history of active peptic ulcer disease should avoid using aspirin, which can cause gastric mucosal irritation, and bleeding.</li> </ul>
<b>Precautions</b>		
General	<ul style="list-style-type: none"> <li>• Aggrenox is not interchangeable with the individual components of aspirin and Persantine® (immediate-release dipyridamole) tablets.</li> <li>• For stroke or TIA patients in whom aspirin is indicated to prevent recurrent myocardial infarction (MI) or angina pectoris, the dose of aspirin in Aggrenox may not provide adequate treatment for the cardiac indications.</li> <li>• <b>Specific to dipyridamole</b>: Because of its dipyridamole component, Aggrenox should be used with caution in patients with coronary artery disease, hepatic insufficiency, and/or hypotension.</li> <li>• <b>Specific to aspirin</b>: Avoid aspirin in patients with severe renal failure (glomerular filtration rate &lt; 10 mL/minute).</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Renal Failure</i>: Aspirin is to be avoided in patients with severe renal failure (glomerular filtration rate &lt; 10 mL/min).</li> <li>• <i>Hepatic Insufficiency</i>: Aspirin is to be avoided in patients with severe hepatic insufficiency.</li> <li>• <i>Sodium Restricted Diets</i>: Sodium-containing buffered aspirin products should be avoided in patients with sodium-retaining states, such as congestive heart failure or renal failure.</li> </ul>
Information to patients	Physicians should inform patients about the signs and symptoms of GI side effects and what steps to take if they occur.	Physicians should inform patients about the signs and symptoms of GI side effects and what steps to take if they occur.
Carcinogenesis	In a 111-week oral study in mice and in a 128-142-week oral study in rats, dipyridamole produced no significant carcinogenic effects at doses of 8, 25 and 75 mg/kg. The high dose exceeded the recommended human daily dose (8 mg/kg) by approximately 9 fold for a 50 kg person.	Administration of aspirin for 68 weeks at 0.5% in the feed of rats was not carcinogenic.
Mutagenesis	<p><b>Aspirin</b>: Aspirin induced chromosome aberrations in cultured human fibroblasts.</p> <p><b>Combination of Dipyridamole and Aspirin</b>: Mutagenicity testing with combination of</p>	In the Ames Salmonella assay, aspirin was not mutagenic, however aspirin did induce chromosome aberrations in cultured human fibroblasts.

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	dipyridamole and aspirin in a ratio of 1:5 revealed no mutagenic potential in the Ames test, in vivo chromosome aberration tests in mice and hamsters, oral micronucleus tests in mice and hamsters and dominant lethal test in mice.	
Fertility impairment	<p><b>Dipyridamole:</b> Reproduction studies with dipyridamole revealed no evidence of impaired fertility in rats at oral dosages of up to 500 mg/kg/day (62 times the recommended human dose). A significant reduction in number of corpora lutea with consequent reduction in implantations and live fetuses was observed at dose of dipyridamole of 1250 mg/kg/day in rats (156 times the recommended human dose on a mg/kg basis).</p> <p><b>Aspirin:</b> Aspirin inhibits ovulation in rats.</p> <p><b>Combination of Dipyridamole and Aspirin:</b> Reproduction studies performed with a combination of dipyridamole and aspirin in a ratio of 1:4.4 in rats and rabbits have revealed no teratogenic evidence at doses of up to 405 (75 + 330) mg/kg/day in rats and 135 (25 +110) mg/kg/day in rabbits. However, treatment with the combination of dipyridamole and aspirin at 405 mg/kg/day induced abortion in rats. In these studies, aspirin itself was teratogenic at doses of 330 mg/kg/day in rats (spina bifida, exencephaly, microphthalmia, and coelosomia) and 110 mg/kg/day in rabbits (congested fetuses, agenesis of skull and upper jaw, generalized edema with malformation of the head, and diaphanous skin). The doses of aspirin at 330 mg/kg/day in rats and at 110 mg/kg/day in rabbits were 330 and 110 times the recommended human dose respectively on a mg/kg basis.</p>	Aspirin inhibits ovulation in rats.
Pregnancy category	<p><b>Dipyridamole:</b> Pregnancy Category B</p> <p><b>Aspirin:</b> Pregnancy Category D</p> <ul style="list-style-type: none"> <li>• Aggrenox should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.</li> <li>• Due to the aspirin component, Aggrenox should be avoided in the third trimester of pregnancy.</li> <li>• Studies of Aggrenox excretion in milk, and potential neonatal drug exposure, have not been conducted. However, because many drugs are excreted in human milk, caution should be exercised when Aggrenox is administered to a nursing woman.</li> </ul>	<p>Pregnancy Category D</p> <ul style="list-style-type: none"> <li>• Pregnant women should only take aspirin if clearly needed. Because of the known effects of NSAIDs on the fetal cardiovascular system (closure of the ductus arteriosus), use during the third trimester of pregnancy should be avoided. Salicylate products have also been associated with alterations in maternal and neonatal hemostasis mechanisms, decreased birth weight, and with perinatal mortality.</li> <li>• Aspirin should be avoided one week prior to and during labor and delivery because it can result in excessive blood loss at delivery. Prolonged gestation and labor due to prostaglandin inhibition have been reported.</li> <li>• Nursing mothers should avoid using aspirin because salicylate is excreted in breast milk. Use of high doses may lead to rashes, platelet abnormalities, and bleeding in nursing infants.</li> </ul>

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<b>Adverse Experience</b>		
Safety experience	<ul style="list-style-type: none"> <li>Evaluated in 6602 patients enrolled in a 24-month, multicenter, double-blind, randomized study (ESPS2).</li> <li>Discontinuation due to adverse events was comparable across treatment groups → 25% (AGG), 25% (ERDP), 19% (ASA), 21% (placebo) (<math>p &lt; 0.001</math> for overall comparison)</li> </ul>	<ul style="list-style-type: none"> <li>Many adverse reactions due to aspirin are dose related.</li> <li>Adverse events are predominantly restricted to GI complications (abdominal pain, heartburn, nausea/vomiting, GI bleeding).</li> <li>At high doses (i.e., plasma levels of greater than 200 mg/mL), the incidence of toxicity increases.</li> </ul>
Adverse events	<p>Adverse events that occurred in <math>\geq 1\%</math> of patients treated with Aggrenox where the incidence was also greater than placebo-treated patients (ESPS-2):</p> <ul style="list-style-type: none"> <li>Headache → 39.2% (AGG), 38.3% (ERDP), 33.8% (ASA), 32.9% (placebo)</li> <li>Dyspepsia → 18.4% (AGG), 17.4% (ERDP), 18.1% (ASA), 16.7% (placebo)</li> <li>Abdominal pain → 17.5% (AGG), 15.4% (ERDP), 15.9% (ASA), 14.5% (placebo)</li> <li>Nausea → 16.0% (AGG), 15.4% (ERDP), 12.7% (ASA), 14.1% (placebo)</li> <li>Diarrhea → 12.7% (AGG), 15.5% (ERDP), 6.8% (ASA), 9.8% (placebo)</li> <li>GI bleeding → 4.1% (AGG), 2.2% (ERDP), 3.2% (ASA), 2.1% (placebo)</li> <li>Intracranial hemorrhage → 0.6% (AGG), 0.5% (ERDP) 0.4% (ASA), 0.4% (placebo)</li> </ul>	<ul style="list-style-type: none"> <li>Patients treated with low-dose aspirin (75-300 mg) are at a two-fold increased risk of upper GI bleeding and perforation.<sup>1</sup></li> </ul>
<b>Interactions</b>		
Drug/Drug Interactions	<ul style="list-style-type: none"> <li><i>Adenosine</i>: Dipyridamole has been reported to increase the plasma levels and cardiovascular effects of adenosine. Adjustment of adenosine dosage may be necessary.</li> <li><i>ACE Inhibitors</i>: Due to the indirect effect of aspirin on the renin-angiotensin conversion pathway, the hyponatremic and hypotensive effects of ACE inhibitors may be diminished by concomitant administration of aspirin.</li> <li><i>Acetazolamide</i>: Concurrent use of aspirin and acetazolamide can lead to high serum concentrations of acetazolamide (and toxicity) due to competition at the renal tubule for secretion.</li> <li><i>Anticoagulant Therapy (heparin and warfarin)</i>: Patients on anticoagulation therapy are at increased risk for bleeding because of effects on platelets. Aspirin can displace warfarin from protein binding sites, leading to prolonged prothrombin time and the bleeding time. Aspirin can increase the anticoagulant activity of heparin, increasing bleeding risk.</li> <li><i>Anticonvulsants</i>: Salicylic acid can displace protein-bound phenytoin and valproic acid, leading to a decrease in the total concentration of phenytoin and an increase in serum valproic acid levels.</li> <li><i>Beta Blockers</i>: The hypotensive effects of beta blockers may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow and salt and fluid retention.</li> <li><i>Cholinesterase Inhibitors</i>: Dipyridamole may counteract the anticholinesterase effect of cholinesterase inhibitors, thereby potentially aggravating myasthenia gravis.</li> <li><i>Diuretics</i>: The effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow and salt and fluid retention.</li> <li><i>Methotrexate</i>: Salicylate can inhibit renal clearance of methotrexate, leading to bone</li> </ul>	<ul style="list-style-type: none"> <li><i>ACE Inhibitors</i>: Due to the indirect effect of aspirin on the renin-angiotensin conversion pathway, the hyponatremic and hypotensive effects of ACE inhibitors may be diminished by concomitant administration of aspirin.</li> <li><i>Acetazolamide</i>: Concurrent use of aspirin and acetazolamide can lead to high serum concentrations of acetazolamide (and toxicity) due to competition at the renal tubule for secretion.</li> <li><i>Anticoagulant Therapy (heparin and warfarin)</i>: Patients on anticoagulation therapy are at increased risk for bleeding because of effects on platelets. Aspirin can displace warfarin from protein binding sites, leading to prolonged prothrombin time and the bleeding time. Aspirin can increase the anticoagulant activity of heparin, increasing bleeding risk.</li> <li><i>Anticonvulsants</i>: Salicylic acid can displace protein-bound phenytoin and valproic acid, leading to a decrease in the total concentration of phenytoin and an increase in serum valproic acid levels.</li> <li><i>Beta Blockers</i>: The hypotensive effects of beta blockers may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow and salt and fluid retention.</li> <li><i>Diuretics</i>: The effectiveness of diuretics in patients with underlying renal or cardiovascular disease may be diminished by the concomitant administration of aspirin due to inhibition of renal prostaglandins, leading to decreased renal blood flow and salt and fluid retention.</li> <li><i>Methotrexate</i>: Salicylate can inhibit renal clearance of methotrexate, leading to bone marrow toxicity, especially in the elderly or renal impaired.</li> <li><i>NSAIDs</i>: The concurrent use of aspirin with other NSAIDs may increase bleeding or lead to decreased renal function.</li> </ul>

<sup>1</sup> Adverse events (AEs) and drug interactions observed with both low and high-dose aspirin are reported here. However, some effects have been shown to be dose-dependent; AEs seen with high doses are also expected to be seen with lower doses but at lesser rates.

	<b>AGGRENOX® (aspirin/extended release dipyridamole)</b>	<b>ASPIRIN (acetylsalicylic acid)</b>
	<p>marrow toxicity, especially in the elderly or renal impaired.</p> <ul style="list-style-type: none"> <li>• <i>NSAIDs</i>: The concurrent use of aspirin with other NSAIDs may increase bleeding or lead to decreased renal function.</li> <li>• <i>Oral Hypoglycemics</i>: Moderate doses of aspirin may increase the effectiveness of oral hypoglycemic drugs, leading to hypoglycemia.</li> <li>• <i>Uricosuric Agents (probenecid and sulfinpyrazone)</i>: Salicylates antagonize the uricosuric action of uricosuric agents.</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Oral Hypoglycemics</i>: Moderate doses of aspirin may increase the effectiveness of oral hypoglycemic drugs, leading to hypoglycemia.</li> <li>• <i>Uricosuric Agents (probenecid and sulfinpyrazone)</i>: Salicylates antagonize the uricosuric action of uricosuric agents</li> <li>• <i>Corticosteroids</i>: concomitant administration with aspirin may increase risk of GI ulceration and reduce serum salicylate levels.</li> <li>• <i>Pyrazolone Derivatives (phenylbutazone, oxyphenbutazone, and possibly dipyrone)</i>: Concomitant administration with aspirin may increase risk of GI ulceration.</li> <li>• <i>Urinary Alkalizers</i>: Decrease effectiveness of aspirin by increasing rate of salicylate renal excretion.</li> <li>• <i>Phenobarbital</i>: Effectiveness of aspirin may be decreased by enzyme induction with concomitant phenobarbital administration.</li> <li>• <i>Antacids</i>: Concurrent administration of absorbable antacids at therapeutic doses may increase the clearance of salicylates in some individuals. The concurrent administration of non-absorbable antacids may alter the rate of absorption of aspirin, thereby resulting in a decreased acetylsalicylic acid/salicylate ratio in plasma. The clinical significance of these decreases in available aspirin is unknown. Enteric coated aspirin should not be given concurrently with antacids, since an increase in the pH of the stomach may affect enteric coating of the tablets.</li> </ul>
Drug/laboratory test interactions	<p><b>Dipyridamole</b>: Dipyridamole has been associated with elevated hepatic enzymes.</p> <p><b>Aspirin</b>: Aspirin has been associated with elevated hepatic enzymes, blood urea nitrogen and serum creatinine, hyperkalemia, proteinuria and prolonged bleeding time.</p>	<ul style="list-style-type: none"> <li>• Aspirin has been associated with elevated hepatic enzymes, blood urea nitrogen and serum creatinine, hyperkalemia, proteinuria, and prolonged bleeding time.</li> </ul>

<sup>1</sup> Adverse events (AEs) and drug interactions observed with both low and high-dose aspirin are reported here. However, some effects have been shown to be dose-dependent; AEs seen with high doses are also expected to be seen with lower doses but at lesser rates.

	<b>PLAVIX® (clopidogrel bisulfate)</b>	<b>TICLID® (ticlopidine)</b>
<b>Chemical formula</b>	methyl (+)-(S)-a -(2-chlorophenyl)-6,7-dihydrothieno[3,2-c]pyridine-5(4H)-acetate sulfate	5-[(2-chlorophenyl)methyl]-4,5,6,7-tetrahydrothieno [3,2-c] pyridine hydrochloride.
<b>Empirical formula</b>	C <sub>16</sub> H <sub>16</sub> ClNO <sub>2</sub> SH <sub>2</sub> SO <sub>4</sub>	Empirical formula not provided in package insert
<b>Molecular weight</b>	419.9	300.25
<b>Available formulations and indicated strengths</b>	One tablet contains 97.875 mg of clopidogrel bisulfate (molar equivalent of 75 mg clopidogrel base). Dosing recommendations are: <ul style="list-style-type: none"> <li>Recent MI, stroke, or established peripheral arterial disease (PAD) → 75 mg once daily.</li> <li>Acute Coronary Syndrome (unstable angina/ non-Q wave MI)→ initiate with a single 300 mg loading dose, then continue with 75 mg once daily. Aspirin (75 mg-325 mg once daily) should be initiated and continued in combination.</li> </ul>	One tablet contains 250 mg of ticlopidine hydrochloride. Dosing recommendations are: <ul style="list-style-type: none"> <li>Stroke: 250 mg bid taken with food.</li> <li>Coronary Artery Stenting: 250 mg bid taken with food together with antiplatelet doses of aspirin for up to 30 days of therapy following successful stent implantation.</li> </ul>
<b>Indications</b>	Plavix is indicated to reduce the rate of a combined endpoint of: <ul style="list-style-type: none"> <li>new ischemic stroke (fatal or not), new MI (fatal or not), and other vascular death in patients with a history of recent myocardial infarction (MI), recent stroke, or established peripheral arterial disease.</li> <li>cardiovascular death, MI, or stroke as well as the rate of a combined endpoint of cardiovascular death, MI, stroke, or refractory ischemia in patients with acute coronary syndrome (unstable angina/non-Q-wave MI) including those who are managed medically and with PTCA or CABG.</li> </ul>	Ticlid is indicated: <ul style="list-style-type: none"> <li>to reduce the risk of thrombotic stroke (fatal or non-fatal) in patients who have experienced stroke precursors or a completed thrombotic stroke.</li> <li>as adjunctive therapy with aspirin to reduce the incidence of subacute stent thrombosis in patients undergoing successful coronary stent implantation.</li> </ul>
<b>Clinical Pharmacology</b>		
<b>Mechanism of action</b>	Inhibits platelet aggregation by selectively and irreversibly inhibiting the binding of adenosine diphosphate (ADP) to its platelet receptor preventing activation of the glycoprotein IIb/IIIa complex. Biotransformation of clopidogrel is necessary to inhibit platelet aggregation, but an active metabolite responsible for the activity of clopidogrel has not been isolated.	Inhibits platelet function and prolongs bleeding time by irreversibly inhibiting ADP-induced platelet-fibrinogen and subsequent platelet-platelet interactions
<b>Pharmacokinetics</b>		
<b>Absorption</b>	Clopidogrel is rapidly absorbed after oral administration of repeated doses of 75 mg clopidogrel (base), with peak plasma levels (3 mg/L) of the main circulating metabolite occurring approximately 1 hour after dosing. After repeated 75-mg oral doses of clopidogrel (base), plasma concentrations of the parent compound, which has no platelet inhibiting effect, are very low and are generally below the quantification limit (0.00025 mg/L) beyond 2 hours after dosing.	Ticlopidine hydrochloride is rapidly absorbed (>80%) after oral administration of a single 250-mg dose. Peak plasma levels occur at approximately 2 hours after dosing.
<b>Food Effects</b>	Administration of clopidogrel with meals did not significantly modify the bioavailability of clopidogrel.	The oral bioavailability of ticlopidine is increased by 20% when taken after a meal. Administration of ticlopidine with food is recommended to maximize gastrointestinal tolerance.

	<b>PLAVIX® (clopidogrel bisulfate)</b>	<b>TICLID® (ticlopidine)</b>
Metabolism	<i>In vitro</i> and <i>in vivo</i> , clopidogrel undergoes rapid hydrolysis into its carboxylic acid derivative. In plasma and urine, the glucuronide of the carboxylic acid derivative is also observed. Clopidogrel is extensively metabolized by the liver. The main circulating metabolite is the carboxylic acid derivative, which has no effect on platelet aggregation. It represents about 85% of the circulating drug-related compounds in plasma.	Ticlopidine hydrochloride is metabolized extensively by the liver; only trace amounts of intact drug are detected in the urine. Ticlopidine hydrochloride displays nonlinear pharmacokinetics and clearance decreases markedly on repeated dosing.
Half-life	The elimination half-life of the main circulating metabolite is 8 hours after single and repeated administration. Covalent binding to platelets accounted for 2% of radiolabel with a half-life of 11 days.	In older volunteers the apparent half-life of ticlopidine after a single 250-mg dose is about 12.6 hours. With repeat dosing (250 mg bid) the terminal elimination half-life rises to 4 to 5 days. Steady-state levels of ticlopidine hydrochloride in plasma are obtained after approximately 14 to 21 days.
Volume of distribution	Absorption is at least 50% based on urinary excretion of clopidogrel-related metabolites. Clopidogrel and the main circulating metabolite bind reversibly <i>in vitro</i> to human plasma proteins (98% and 94%, respectively). The binding is non-saturable <i>in vitro</i> up to a concentration of 100 µg/mL.	Ticlopidine hydrochloride binds reversibly (98%) to plasma proteins, mainly to serum albumin and lipoproteins. The binding to albumin and lipoproteins is nonsaturable over a wide concentration range. Ticlopidine also binds to alpha-1 acid glycoprotein. At concentrations attained with the recommended dose, only 15% or less ticlopidine in plasma is bound to this protein.
Excretion	Following an oral dose of <sup>14</sup> C-labeled clopidogrel in humans, approximately 50% was excreted in the urine and approximately 46% in the feces in the 5 days after dosing.	Following an oral dose of radioactive ticlopidine hydrochloride administered in solution, 60% of the radioactivity is recovered in the urine and 23% in the feces. Ticlopidine hydrochloride is a minor component in plasma (5%) after a single dose, but at steady-state is the major component (15%).
Special populations	<ul style="list-style-type: none"> <li>• <i>Geriatric Patients</i>: Plasma concentrations of the main circulating metabolite of clopidogrel are significantly higher in elderly (≥75 years) compared to healthy volunteers, but these higher plasma levels were not associated with differences in platelet aggregation and bleeding time. No dosage adjustment is needed.</li> <li>• <i>Pediatric patients</i>: Safety and effectiveness in pediatric patients have not been studied.</li> <li>• <i>Renal dysfunction</i>: No dosage adjustment is necessary for patients with renal disease. Inhibition of ADP-induced platelet aggregation was lower (25%) than that observed in healthy volunteers, but the prolongation of bleeding time was similar.</li> <li>• <i>Gender</i>: No significant difference was observed in the plasma levels of the main circulating metabolite between males and females.</li> <li>• <i>Race</i>: Pharmacokinetic differences due to race have not been studied.</li> </ul>	<ul style="list-style-type: none"> <li>• <i>Geriatric Patients</i>: Clearance of ticlopidine decreases with age. Steady-state trough values in elderly patients (mean age 70 years) are about twice those in younger volunteer populations.</li> <li>• <i>Pediatric patients</i>: Safety and effectiveness in pediatric patients have not been studied.</li> <li>• <i>Hepatically Impaired Patients</i>: Because of limited experience in patients with severe hepatic disease, who may have bleeding diatheses, the use of ticlopidine is not recommended in this population.</li> <li>• <i>Renally Impaired Patients</i>: It may be necessary to reduce the dosage of ticlopidine or discontinue it altogether if hemorrhagic or hematopoietic problems are encountered.</li> </ul>
Contraindications	Plavix is contraindicated in patients with: <ul style="list-style-type: none"> <li>• hypersensitivity to the drug substance or any component of the product,</li> <li>• active pathological bleeding such as peptic ulcer or intracranial hemorrhage.</li> </ul>	Ticlid is contraindication in the following conditions: <ul style="list-style-type: none"> <li>• hypersensitivity to the drug,</li> <li>• presence of hematopoietic disorders (e.g., neutropenia and thrombocytopenia, past history of either TTP or aplastic anemia),</li> <li>• presence of a hemostatic disorder or active pathological bleeding (e.g., bleeding peptic ulcer or intracranial bleeding),</li> <li>• patients with severe liver impairment</li> </ul>
Warnings	<i>Thrombotic Thrombocytopenic Purpura (TTP)</i> : rare reports following use of clopidogrel, sometimes after a short exposure (<2weeks). TTP was not seen during clinical trials, which included over 17,500 clopidogrel-treated patients. In world-wide post-marketing experience, TTP has been reported at a rate of about four cases per million patients exposed, or about 11	Ticlopidine can cause life-threatening hematological AEs including: <ul style="list-style-type: none"> <li>• <i>Neutropenia/Agranulocytosis</i>: 50 cases (2.4%) of neutropenia (&lt;1200 neutrophils/mm<sup>3</sup>) among 2048 stroke patients in clinical trials. The incidence peaks at approximately 4-6 weeks of therapy.</li> </ul>

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	cases per million patient-years. The background rate is thought to be about four cases per million person-years.	<ul style="list-style-type: none"> <li>• <i>TTP</i>: One case of TTP was reported during clinical trials in stroke patients. Based on post-marketing data, US physicians reported about 100 cases between 1992 and 1997. Based on an estimated patient exposure of 2 to 4 million and event-reporting rate of 10%, the incidence of TTP may be as high as 1 in every 2000 - 4000 patients exposed. The incidence peaks after 3-4 weeks of therapy.</li> <li>• <i>Aplastic Anemia</i>: Aplastic anemia was not seen during clinical trials in stroke patients, but US physicians reported about 50 cases between 1992 and 1998. Given the prior assumptions, the incidence of aplastic anemia may be as high as 1 in every 4000 - 8000 patients exposed. The incidence of aplastic anemia peaks after 4-8 weeks of therapy.</li> </ul>
<b>Precautions</b>		
General	<ul style="list-style-type: none"> <li>• Clopidogrel prolongs bleeding time and should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions (i.e., GI ulcers and intraocular conditions). Drugs that induce or exacerbate such lesions should be used with caution in patients taking clopidogrel.</li> <li>• Clopidogrel should be discontinued 5 days prior to surgery if a patient is to undergo elective surgery and an antiplatelet effect is not desired.</li> <li>• Clopidogrel should be used with caution in patients with hepatic and/or renal dysfunction.</li> </ul>	<ul style="list-style-type: none"> <li>• Ticlopidine prolongs bleeding time and should be used with caution in patients who may be at risk of increased bleeding from trauma, surgery, or other pathological conditions (i.e., GI ulcers and intraocular conditions). Drugs that induce or exacerbate such lesions should be used with caution in patients taking ticlopidine.</li> <li>• Ticlopidine should be discontinued 10-14 days prior to surgery if a patient is to undergo elective surgery and an antiplatelet effect is not desired.</li> <li>• The use of ticlopidine is not recommended in patients with severe hepatic disease.</li> <li>• Dose adjustments or drug discontinuation may be necessary in patients with renal dysfunction if hemorrhagic or hematopoietic problems are seen.</li> </ul>
Information to patients	<ul style="list-style-type: none"> <li>• Patients should be told that it may take them longer than usual to stop bleeding when they take clopidogrel.</li> <li>• Patients should report any unusual bleeding to their physician.</li> <li>• Patients should inform physicians and dentists that they are taking Plavix before any surgery is scheduled and before any new drug is taken.</li> </ul>	<ul style="list-style-type: none"> <li>• Patients should be told that neutropenia or thrombocytopenia can occur, especially during the first 3 months of treatment and that severe neutropenia can result in an increased risk of infection.</li> <li>• Patients should be told to obtain scheduled blood tests to detect neutropenia or thrombocytopenia.</li> <li>• Patients should contact their physicians if they experience any indication of infection such as fever, chills, or sore throat, which may be a consequence of neutropenia.</li> <li>• Symptoms and signs of TTP, such as fever, weakness, difficulty speaking, seizures, yellowing of skin or eyes, dark or bloody urine, pallor or petechiae (pinpoint hemorrhagic spots on the skin), should be reported immediately.</li> <li>• All patients should be told that it may take them longer than usual to stop bleeding when they take ticlopidine and that they should report any unusual bleeding to their physician.</li> <li>• Patients should tell physicians and dentists that they are taking ticlopidine before any surgery is scheduled and before any new drug is prescribed.</li> <li>• Patients should promptly report side effects (e.g., severe or persistent diarrhea, skin rashes, subcutaneous bleeding, any signs of cholestasis, such as yellow skin or sclera, dark urine, or light-colored stools).</li> <li>• Patients should be told to take ticlopidine with food or just after eating in order to minimize gastrointestinal discomfort.</li> </ul>
Carcinogenesis	There was no evidence of tumorigenicity when clopidogrel was administered for 78 weeks to mice and 104 weeks to rats at dosages up to 77 mg/kg per day, leading to plasma exposures >25	<ul style="list-style-type: none"> <li>• In a 2-year oral carcinogenicity study in rats, ticlopidine at daily doses of up to 100 mg/kg (610 mg/m<sup>2</sup>) was not tumorigenic. This dose is 14 times the recommended</li> </ul>

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	times that in humans at the recommended daily dose of 75 mg.	clinical dose for a 70 kg person. <ul style="list-style-type: none"> <li>In a 78-week oral carcinogenicity study in mice, ticlopidine at daily doses up to 275 mg/kg (1180 mg/m<sup>2</sup>) was not tumorigenic. This dose is 40 times the recommended clinical dose on a mg/kg basis and four times the clinical dose on a body surface area basis.</li> </ul>
Mutagenesis	Clopidogrel was not genotoxic in four <i>in vitro</i> tests (Ames test, DNA-repair test in rat hepatocytes, gene mutation assay in Chinese hamster fibroblasts, and metaphase chromosome analysis of human lymphocytes) and in one <i>in vivo</i> test (micronucleus test by oral route in mice).	Ticlopidine was not mutagenic <i>in vitro</i> in the Ames test, the rat hepatocyte DNA-repair assay, or the Chinese-hamster fibroblast chromosomal aberration test; or <i>in vivo</i> in the mouse spermatozoid morphology test, the Chinese-hamster micronucleus test, or the Chinese-hamster bone-marrow-cell sister-chromatid exchange test.
Fertility impairment	Clopidogrel was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg per day (52 times the recommended human dose on a mg/m <sup>2</sup> basis).	Ticlopidine was found to have no effect on fertility of male and female rats at oral doses up to 400 mg/kg/day.
Pregnancy category	Pregnancy category B  <i>Pregnant women:</i> Reproduction studies performed in rats and rabbits at doses up to 500 and 300 mg/kg/day (respectively, 65 and 78 times the recommended daily human dose on a mg/m <sup>2</sup> basis), revealed no evidence of impaired fertility or fetotoxicity due to clopidogrel. However, there are no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, clopidogrel should be used during pregnancy only if clearly needed.  <i>Nursing mothers:</i> Studies in rats have shown that clopidogrel and/or its metabolites are excreted in the milk but it is unknown if this drug is excreted in human milk. Because many drugs are excreted in human milk with a potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue clopidogrel during nursing.	Pregnancy Category B  <i>Pregnant women:</i> Teratology studies have been conducted in mice (doses up to 200 mg/kg/day), rats (doses up to 400 mg/kg/day) and rabbits (doses up to 200 mg/kg/day). Doses of 400 mg/kg in rats, 200 mg/kg/day in mice and 100 mg/kg in rabbits produced maternal toxicity, as well as fetal toxicity, but there was no evidence of a teratogenic potential of ticlopidine. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of a human response, Ticlid should be used during pregnancy only if clearly needed.  <i>Nursing Mothers:</i> Studies in rats have shown ticlopidine is excreted in the milk. It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk with a potential for serious adverse reactions in nursing infants, a decision should be made whether to discontinue nursing or to discontinue ticlopidine during nursing.
<b>Adverse Experience</b>		
Safety experience	<ul style="list-style-type: none"> <li>Evaluated in &gt; 17,500 patients, including over 9,000 patients treated for 1 year or more (CAPRIE and CURE trials).<sup>2</sup></li> <li>Overall tolerability of clopidogrel in CAPRIE was similar to that of aspirin regardless of age, gender and race.</li> <li>Discontinuations due to AEs were comparable between clopidogrel and aspirin (13%),</li> </ul>	<ul style="list-style-type: none"> <li>Evaluated in &gt;4000 patients treated with ticlopidine, aspirin, or placebo for up to 5.8 years (TASS and CATS trials).</li> <li>Discontinuations due to AEs → 20.9% (Ticlid), 14.5% (ASA), 6.1% (placebo)</li> </ul>
Adverse events	Adverse events that occurred in ≥ 2.5% patients treated with clopidogrel (CAPRIE trial): <ul style="list-style-type: none"> <li>Skin/appendage disorders → 15.8% (PVX) vs. 13.1% (ASA)</li> <li>Headache → 7.6% (PVX) vs. 7.2% (ASA)</li> <li>Abdominal pain → 5.6% (PVX) vs. 7.1% (ASA)</li> <li>Dyspepsia → 5.2% (PVX) vs. 6.1 (ASA)</li> <li>Diarrhea → 4.5% (PVX) vs. 3.4% (ASA)</li> </ul>	Most common AEs occurring in ≥ 1% of patients treated with Ticlid: <ul style="list-style-type: none"> <li>Diarrhea → 8.3% (Ticlid) vs. 1.8% (ASA)</li> <li>Nausea → 7.0% (Ticlid) vs. 6.2% (ASA)</li> <li>Dyspepsia → 7.0% (Ticlid) vs. 9.0% (ASA)</li> <li>Rash → 5.1% (Ticlid) vs. 1.5% (ASA)</li> <li>GI pain → 3.7% (Ticlid) vs. 5.6% (ASA)</li> </ul>

<sup>2</sup> The CAPRIE trial was conducted in patients with recent MI, recent Stroke or established PAD, while CURE was conducted in patients with acute coronary syndrome (i.e., unstable angina/non-Q wave MI). Because Aggrenox is indicated in patients with prior stroke and not acute coronary syndrome, only results from CAPRIE are discussed in this comparison.

	PLAVIX® (clopidogrel bisulfate)	TICLID® (ticlopidine)
	<ul style="list-style-type: none"> <li>Nausea → 3.4% (PVX) vs. 3.8% (ASA)</li> <li>GI hemorrhaging → 2.0% (PVX) vs. 2.7% (ASA)</li> <li>Intracranial hemorrhaging → 0.4% (PVX) vs. 0.5 % (ASA)</li> </ul>	<ul style="list-style-type: none"> <li>Neutropenia → 2.4% (Ticlid) vs. 0.8% (ASA)</li> <li>Purpura → 2.2% (Ticlid) vs. 1.6 % (ASA)</li> </ul>
<b>Interactions</b>		
Drug/Drug Interactions	<ul style="list-style-type: none"> <li><i>Aspirin</i>: Aspirin did not modify the clopidogrel-mediated inhibition of ADP-induced</li> <li><i>Platelet aggregation</i>: Concomitant administration of 500 mg of aspirin twice a day for 1 day did not significantly increase the prolongation of bleeding time induced by clopidogrel.</li> <li><i>Heparin</i>: Clopidogrel did not necessitate modification of the heparin dose or alter the effect of heparin on coagulation. Co-administration of heparin had no effect on inhibition of platelet aggregation induced by clopidogrel.</li> <li><i>NSAIDs</i>: Concomitant administration of clopidogrel was associated with increased occult GI blood loss in healthy volunteers receiving naproxen. NSAIDs and clopidogrel should be co-administered with caution.</li> <li><i>Warfarin</i>: The safety of the co-administration of clopidogrel with warfarin has not been established. Consequently, concomitant administration of these two agents should be undertaken with caution.</li> <li><i>Other concomitant therapy</i>: No clinically significant pharmacodynamic interactions were observed when clopidogrel was co-administered with atenolol, nifedipine, or both. The pharmacodynamic activity of clopidogrel was also not significantly influenced by the co-administration of phenobarbital, cimetidine or estrogen. The pharmacokinetics of digoxin or theophylline were not modified by the co-administration of clopidogrel.</li> <li>Clopidogrel may interfere with the metabolism of phenytoin, tamoxifen, tolbutamide, warfarin, torsemide, fluvastatin, and many non-steroidal anti-inflammatory agents, but there are no data with which to predict the magnitude of these interactions. Caution should be used when any of these drugs is co-administered with clopidogrel.</li> </ul>	<ul style="list-style-type: none"> <li><i>Aspirin and Other NSAIDs</i>: Ticlopidine potentiates the effect of aspirin or other NSAIDs on platelet aggregation. The safety of concomitant use of ticlopidine and NSAIDs has not been established. The safety of concomitant use of ticlopidine and aspirin beyond 30 days has not been established. Caution should be exercised in patients who have lesions with a propensity to bleed, such as ulcers. Long-term concomitant use of aspirin and ticlopidine is not recommended.</li> <li><i>Antacids</i>: Administration of ticlopidine after antacids resulted in an 18% decrease in plasma levels of ticlopidine.</li> <li><i>Cimetidine</i>: Chronic administration of cimetidine reduced the clearance of a single dose of ticlopidine by 50%.</li> <li><i>Digoxin</i>: Coadministration of ticlopidine with digoxin resulted in a 15% decrease in digoxin plasma levels. Little or no change in therapeutic efficacy of digoxin is expected.</li> <li><i>Theophylline</i>: In normal volunteers concomitant administration of ticlopidine resulted in a significant increase in the theophylline elimination half-life from 8.6 to 12.2 hours and a comparable reduction in total plasma clearance of theophylline.</li> <li><i>Phenobarbital</i>: In 6 normal volunteers, the inhibitory effects of ticlopidine on platelet aggregation were not altered by chronic administration of phenobarbital.</li> <li><i>Phenytoin</i>: <i>In vitro</i> studies demonstrated that ticlopidine does not alter the plasma protein binding of phenytoin. Protein binding interactions of ticlopidine and its metabolites have not been studied <i>in vivo</i>. Several cases of elevated phenytoin plasma levels with associated somnolence and lethargy have been reported following coadministration with ticlopidine. Caution should be exercised in co-administering this drug with ticlopidine, and it may be useful to measure phenytoin blood concentrations.</li> <li><i>Propranolol</i>: <i>In vitro</i> studies demonstrated that ticlopidine does not alter the plasma protein binding of propranolol. However, the protein binding interactions of ticlopidine and its metabolites have not been studied <i>in vivo</i>. Caution should be exercised in co-administering this drug with ticlopidine.</li> </ul>
Drug/laboratory test interactions	None known	<ul style="list-style-type: none"> <li><i>Liver Function</i>: Ticlopidine has been associated with elevations of alkaline phosphatase, bilirubin, and transaminases, occurring within 1 to 4 months of therapy initiation. Liver function testing, including ALT, AST, and GGT, should be considered whenever liver dysfunction is suspected, particularly during the first 4 months of treatment.</li> <li><i>Cholesterol</i>: Ticlopidine therapy causes increased serum cholesterol and triglycerides.</li> </ul>

## **2.2 Place of product in therapy**

### **2.2.a *Epidemiology and risk factors***

Stroke ranks as the third leading cause of death in the US, behind cancer and heart disease, and is the leading cause of serious long-term disability (American Stroke Association, 2002). More than 700,000 new or recurrent strokes occur annually, and approximately 4,000,000 Americans are currently living with neurologic deficits due to stroke (American Stroke Association, 2002). Secondary stroke accounts for 100,000 deaths annually, which translates into 16.7% of all stroke-related deaths. As Sacco et al. (1997) point out, as mortality from stroke declines, the incidence of secondary stroke is expected to rise. Indeed, 5-14% of individuals suffering a first stroke will have a second stroke, most likely to be ischemic, within one year (Sacco et al., 1997; American Stroke Association, 2002).

Many modifiable and non-modifiable risk factors have been identified for first strokes; most of these factors are also common to secondary strokes (Feinberg, 1996). It is known that the most significant risk factor for recurrent ischemic stroke is a prior stroke (MacMahon & Rodgers, 1994). Recent epidemiologic data (Petty et al., 1998 and Vickrey et al., 2002) and results of large interventional outcome studies (Gent et al., 1989; Hass et al., 1989; CAPRIE Steering Committee, 1996; and Diener et al., 1996) demonstrate that patients who have had a transient ischemic attack (TIA) or stroke have a two- to seven-fold greater risk of having a recurrent stroke rather than a myocardial infarction (MI). Some key modifiable risk factors include hypertension, atrial fibrillation, high cholesterol, diabetes, and poor lifestyle habits (e.g., smoking, alcohol abuse, sedentary lifestyle) (Feinberg, 1996; Sacco et al., 1997; MacMahon & Rodgers, 1994; National Stroke Association, 1999; American Heart Association, 2002). The relative risk associated with lifestyle factors ranges from 1.5 to 3 (Feinberg, 1996), from 4 to 5 for cardiac factors (e.g., hypertension) (Feinberg, 1996), and from 1.5 to 23.5 for atrial fibrillation (Sacco et al., 1997). Some non-modifiable factors include age > 65, male gender, African-American race, family history of stroke or TIA, and personal history of stroke.

As the prevalence of secondary strokes increases, the level of health care resource utilization for management of secondary strokes subsequently increases. Direct costs (e.g., hospitalization/nursing home stays, physician and home health visits, medications) associated with primary and secondary strokes in 1999 were estimated to be \$29.5 billion in the US (American Heart Association, 2002). Hospitalizations/nursing home stays represent the largest component of direct costs (82.7%). Indirect costs (lost productivity due to morbidity and mortality of stroke) add \$10.8 billion. Furthermore, informal caregiver burden is a significant component of cost, as many stroke survivors require assistance in completing daily activities following a stroke. The total sum attributable to stroke-related death and disability is expected to rise to \$49 billion in 2002 (American Stroke Association, 2002).

### **2.2.b *Pathophysiology***

A stroke occurs when blood flow to an area of the brain is interrupted, due to either a blockage or a breakage of a blood vessel or artery. Computed Tomography (CT) scans are used to classify strokes as either ischemic (blockage of a vessel) or hemorrhagic (breakage of a vessel); indeed, 75-80% of all strokes are ischemic, which can be classified further into embolic and thrombotic

ischemic strokes (Sacco et al., 1997). Regardless of the type of stroke, brain cells in the immediate area where the stroke occurs are destroyed, releasing chemicals that may potentially destroy brain cells in surrounding areas. The extent of brain cell death determines the impairment of abilities linked to damaged parts of the brain (e.g., speech, movement, memory). For example, smaller strokes may lead to limb weakness, whereas larger strokes may lead to paralysis.

### *2.2.c Clinical presentation*

The most common symptoms of stroke include sudden numbness or weakness of the face, arms or legs, especially on one side of the body; sudden confusion, trouble speaking or understanding; sudden trouble seeing in one or both eyes; sudden trouble walking, dizziness, loss of balance or coordination; sudden severe headache with no known cause. Some of the symptoms occurring less frequently are sudden nausea, fever and vomiting with rapid onset (minutes to hours) and brief loss of consciousness. Given the wide array of symptoms, their onset often prevents those suffering from the stroke to realize what is happening; many individuals often delay seeking medical attention. Indeed, 58% of stroke patients don't present until 24 hours or more after the occurrence of stroke (Alberts et al., 1990). According to Feldman et al. (1993), 13 hours is the median time from stroke onset to a patient's presentation to a clinician.

### *2.2.d Approaches to treatment*

Preventing secondary ischemic stroke requires a combination of several factors, including lifestyle changes (e.g., low-fat, low-sodium diets, moderate to little alcohol intake, cessation of smoking, daily exercise) and medical management of other conditions that may have triggered the first stroke (e.g., hypertension, diabetes, high cholesterol). Additionally, certain cerebrovascular (e.g., prior stroke or TIA) and cardiovascular diseases (e.g., atrial fibrillation, angina, prior MI, increased left ventricular mass) that put otherwise-healthy individuals at a greater risk for secondary ischemic stroke must be managed effectively. An algorithm to reduce the risk of secondary stroke is presented in Figure 1 (page 19).

Pharmacotherapy is recommended for patients in whom lifestyle modification does not reduce other medical conditions (e.g., hypertension, high cholesterol, diabetes). ACE-inhibitors, beta-blockers, calcium-channel blockers, angiotensin-II receptor blockers, and diuretics are among the commonly used anti-hypertensive agents that help reduce the risk of primary and recurrent ischemic stroke. Statins and oral hypoglycemic or insulin therapy are popular options to keep cholesterol levels and diabetes under control.

Atherosclerosis of both the small and large arteries that provide blood flow to the brain is the most common cause of cerebral ischemia; however, approximately 20% of all ischemic strokes are due to cardioembolism, most commonly from atrial fibrillation. Therapeutic choices for prevention of ischemic stroke should be guided by the underlying cause and known risk factors. Guidelines for treatment and prevention of ischemic stroke supported by the American College of Chest Physicians (Albers et al., 2001) recommend oral anticoagulant therapy for primary and secondary prevention of cardioembolic stroke in high-risk individuals. While antiplatelet therapy may be more appropriate in patients at low risk for recurrent strokes due to cardioembolic phenomena, strong evidence is lacking to support their efficacy. The American

College of Chest Physicians and the American Heart Association Stroke Council (Albers et al., 2001; Albers et al., 1999; and Wolf et al., 1999) recommend antiplatelet therapy (e.g., aspirin, Aggrenox<sup>®</sup>, Plavix<sup>®</sup>, and Ticlid<sup>®</sup>) for prevention of atherothrombotic stroke or TIA.

Aspirin (prescribed at doses ranging from 30 mg – 1300 mg) was considered the standard of care until recently; trials conducted in the last 5-10 years suggest that Aggrenox<sup>®</sup>, Plavix<sup>®</sup>, and Ticlid<sup>®</sup> are more effective than aspirin in preventing secondary stroke. Indeed, three key trials have been conducted that compare aspirin with an antiplatelet agent in a head-to-head fashion. In the European Stroke Prevention Study 2 (ESPS-2), Aggrenox<sup>®</sup> was shown to be significantly more effective than aspirin in reducing the risks of secondary stroke in patients who had suffered a stroke or completed transient ischemic attack (relative risk reduction versus aspirin 22.1%,  $p=0.0008$ ) (Diener et al., 1996). In the CAPRIE trial (1996), while the combined endpoint of stroke, MI, and vascular death was reduced by Plavix<sup>®</sup> in the total study population comprised of 19,185 patients with a history of ischemic stroke, MI, or peripheral vascular disease (relative risk reduction versus aspirin 8.7%,  $p=0.043$ ), stroke risk was not significantly reduced by Plavix<sup>®</sup> in the subgroup of patients enrolled with a prior stroke within 6 months ( $n=6431$ , relative risk reduction versus aspirin 8%,  $p=0.28$ ). Ticlid was studied in a third trial (Hass et al., 1989) where it was found to reduce the risk of recurrent stroke by 21% ( $p=0.024$ ). Unfortunately, no head-to-head studies have been conducted evaluating the newer antiplatelet agents; therefore only indirect comparisons of the efficacy and safety of these agents can be made (Albers & Tijssen., 1999; Albers, 2000).

#### *2.2.e £Alternative treatment options*

Surgery is recommended in patients with moderate to severe carotid artery stenosis. Carotid endarterectomy, performed to clear fatty deposits and enable the blood to flow more freely, can reduce the risk of secondary stroke by 66% (Lees et al., 2000).

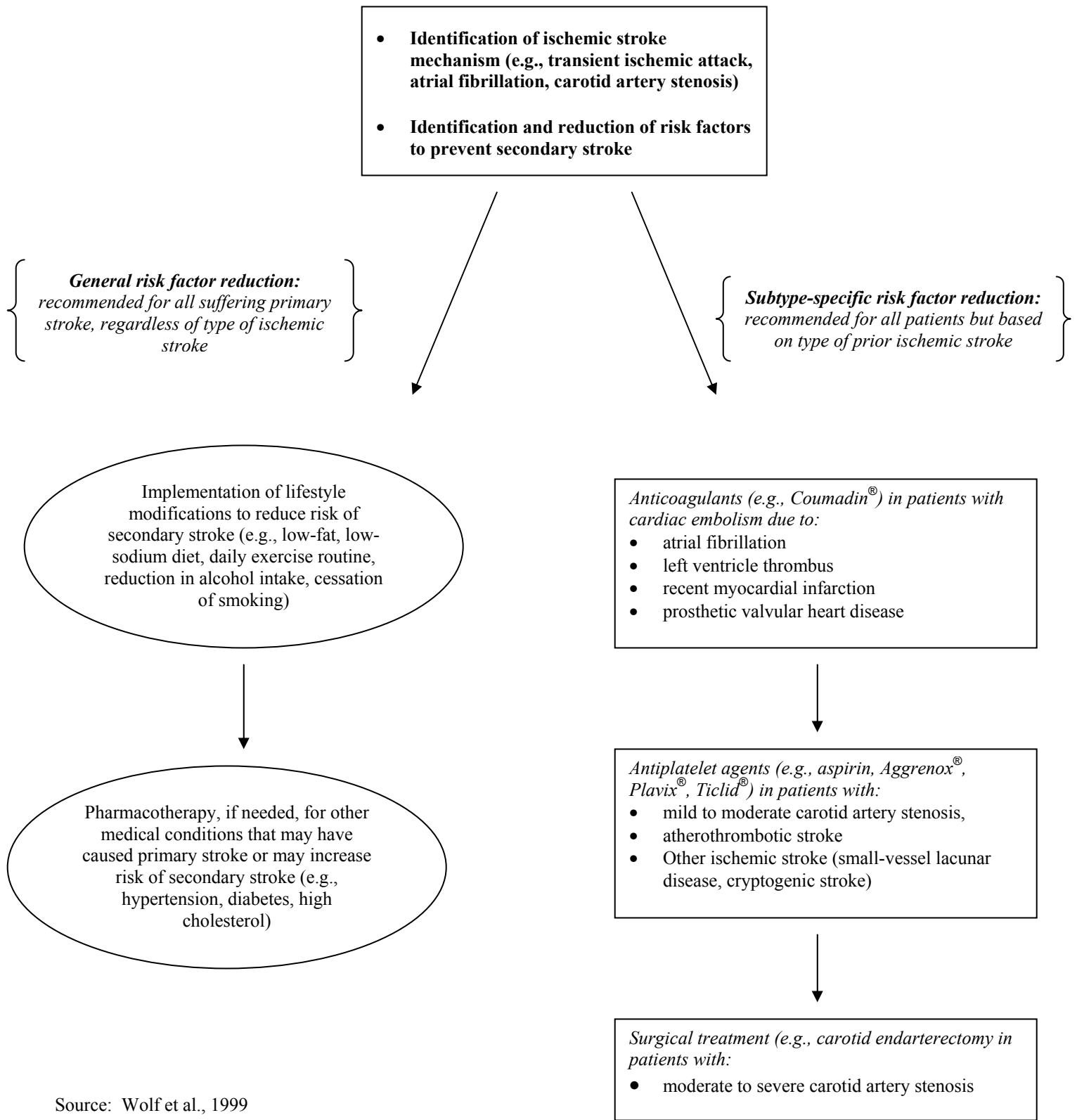
#### *2.2.f £Place of product in therapy*

Aggrenox<sup>®</sup> is indicated to reduce the risk of stroke in patients who have had transient ischemia of the brain or completed ischemic stroke due to thrombosis.

#### *2.2.g £Expected outcomes of therapy*

Based on findings from the European Stroke Prevention Study 2 (ESPS-2), Aggrenox<sup>®</sup> significantly reduced the risk of stroke by 22.1% vs. aspirin ( $p=0.008$ ), 24.4% vs. extended-release dipyridamole alone ( $p=0.002$ ), and 36.8% vs. placebo ( $p<0.001$ ) in patients who had previously suffered an ischemic stroke or TIA (Diener et al., 1996; data on file). In addition to preventing secondary strokes, Aggrenox<sup>®</sup> may be a more cost-effective therapy vs. aspirin, with a cost per stroke avoided ratio of \$28,472 across two years (Shah & Gondek, 2000). Reducing the risk of stroke implies reducing the risk of stroke-related morbidity and mortality, a cost-saving measure that potentially reduces caregiver burden and improves a patient's quality of life.

**Figure 1. Reduction of risk of secondary stroke**



Source: Wolf et al., 1999

### **3.1.1 CLINICAL SUPPORT FOR AGGRENOL<sup>®</sup>**

This section of the dossier provides a review of the clinical evidence for Aggrenol<sup>®</sup> (aspirin/extended-release dipyridamole). Section 3.1 discusses the efficacy and safety of Aggrenol<sup>®</sup>. Section 3.2 discusses the cost-effectiveness of Aggrenol<sup>®</sup> compared with other antiplatelet therapies.

#### **3.1 Efficacy and safety support of Aggrenol<sup>®</sup>**

##### *3.1.a Evolution of combination therapy with dipyridamole plus aspirin*

Although the dose of Aggrenol<sup>®</sup> approved by the FDA has been studied in only one trial, combination therapy of dipyridamole and aspirin has been studied in fifteen trials. Results of early clinical trials to evaluate the efficacy of dipyridamole and aspirin for prevention of secondary stroke were extremely dissimilar due to disparate study designs and the small numbers of patients studied. The European Stroke Prevention Study 1 (ESPS-1) was the first study with a sufficient patient population to demonstrate the potential benefit of the combination of dipyridamole (immediate-release formulation) and aspirin for the prevention of secondary stroke for patients with prior ischemic stroke or TIAs (ESPS Group, 1990). Enrollees in this trial were restricted to those who had suffered a prior cerebrovascular disorder (e.g., TIA, reversible ischemic neurologic deficit (RIND), or completed ischemic stroke). Results from this large multicenter study (n=2500 patients) suggested that this drug combination led to a significant reduction in secondary stroke versus placebo (38.1%,  $p<0.001$ ). However, unanswered questions remained regarding the contribution made by dipyridamole and aspirin individually, as well as the most appropriate doses of dipyridamole and aspirin required for efficacy while minimizing gastrointestinal and bleeding side effects.

The European Stroke Prevention Study 2 (ESPS-2) was developed to determine the efficacy of combination therapy with aspirin and dipyridamole (extended-release formulation). Dose selection for this trial was based on several clinical pharmacological studies (Müller et al., 1990; data on file, Boehringer Ingelheim). Results from early trials of dipyridamole and aspirin indicated that both dipyridamole and aspirin inhibit platelet aggregation. However, mechanisms of actions for the two drugs are different, making their effects additive. Results further confirmed that inhibition of platelets could be achieved with lower, less toxic doses of aspirin (Johnson., 1999; Algra & van Gijn., 1996; Tijssen JGP., 1998) and higher doses of dipyridamole, administered via an extended-release formulation (data on file, Boehringer Ingelheim). These results led to the evaluation of Aggrenol<sup>®</sup> (combined extended-release dipyridamole 200 mg and immediate-release aspirin 25 mg) in a large-scale (n=6602) trial. ESPS-2 was designed to compare the efficacy of Aggrenol<sup>®</sup> with monotherapies of extended-release dipyridamole 200 mg and aspirin 25 mg in subjects who had suffered a prior completed ischemic stroke or TIA. ESPS-2 is discussed in greater detail in Section 3.1.c.

##### *3.1.b Immediate-Release vs. Extended-Release Dipyridamole*

The dose and formulation of extended-release dipyridamole in Aggrenol<sup>®</sup> was developed to optimize antiplatelet efficacy by compensating for pH-dependent solubility and prolonging

exposure to therapeutic concentrations of dipyridamole. Each extended-release dipyridamole pellet consists of a tartaric acid core surrounded by a layer of dipyridamole and a coating of polymeric, gastrointestinal pH-dependent, retardant lacquer. The purpose of the tartaric acid is to provide an acidic micro-environment for improved dissolution of the encased dipyridamole, regardless of the location of the pellet within the gastrointestinal tract and the associated gastrointestinal pH. As a result, the absorption profile of extended-release dipyridamole is more consistent and reproducible than immediate-release dipyridamole. Additionally, the frequency of dosing could be reduced from four times a day to twice daily, improving patient convenience and compliance as compared with immediate-release dipyridamole tablets (data on file, Boehringer Ingelheim).

Dipyridamole kinetics are linear and similar between single and multiple-dose administration regardless of formulation. However, trough concentrations of the extended-release formulation of dipyridamole are notably higher following multiple dosing than those predicted from single-dose administration. These deviations may be attributable to enterohepatic recycling and/or diurnal variations. Steady-state concentrations are achieved by 48 hours following administration of either extended-release dipyridamole 200 mg twice daily or immediate-release dipyridamole 100 mg four times a day. The pharmacokinetic profiles of extended-release and immediate-release dipyridamole differ primarily in their rate and extent of absorption (data on file, Boehringer Ingelheim).

Based on data from pharmacokinetic studies in healthy male and female volunteers with normal gastric pH (data on file, Boehringer Ingelheim), the absolute bioavailability of the extended-release formulation of dipyridamole in Aggrenox<sup>®</sup> is approximately 70%; with the 30% loss of dipyridamole resulting from a first-pass effect in the liver. After administration of Aggrenox<sup>®</sup>, steady state plasma concentrations of dipyridamole rise after a lag-time of about 30 minutes, form a broad peak with  $T_{max}$  at approximately 2 hours, and then decline slowly over the remainder of the dosing interval. After administration of immediate-release dipyridamole, steady state plasma concentrations of dipyridamole rise after a short lag-time, form a sharp peak with  $T_{max}$  at approximately 0.75 hours, and then decline rapidly. While the extent of absorption of dipyridamole was similar after administration of Aggrenox<sup>®</sup> and immediate-release dipyridamole tablets, the rate and maintenance of absorption with Aggrenox<sup>®</sup> was superior to immediate-release dipyridamole tablets, as evident from the 15% lower peak to trough fluctuations (8% lower peak concentrations and 23% higher trough concentrations).

These studies did not address the issue of the poor absorption of immediate-release dipyridamole in an elderly patient population, representative of the population for which Aggrenox<sup>®</sup> is indicated for secondary stroke prevention. In vitro studies have demonstrated that dipyridamole, a weak base ( $pK_a=6.4$ ), has substantially lower solubility at gastric  $pH>4$  than at physiologic gastric  $pH<3$  (data on file). The incidence of achlorhydria in the elderly ( $>60$  years of age) has been estimated to be as high as 31% (Krasinski et al., 1986). A more recent study found that only 9% of elderly individuals ( $>65$  years of age) had atrophic gastritis, but reported consistent (11%) or intermittent (22%) gastric acid hyposecretion with a gastric pH above 3.5 for almost every third subject (Hurwitz A et al., 1997). In addition, the widespread use of gastric acid modifying prescription and non-prescription medications (antacids, histamine ( $H_2$ ) blockers, and

proton pump inhibitors) increase the proportion of elderly individuals with at least temporarily elevated gastric pH levels.

A recent study (VanderMaelen CP., 2002) demonstrated that absorption of dipyridamole over the 12-hour dosing interval was reduced by 53% when the immediate-release dipyridamole plus aspirin was substituted for Aggrenox<sup>®</sup> in individuals with reduced gastric acidity. Similarly, the average peak concentration of dipyridamole was reduced by 57% when regimen containing immediate-release dipyridamole was substituted for Aggrenox<sup>®</sup>. These recent pharmacokinetic findings corroborate FDA recommendations, found in both the “PRECAUTIONS” and “DOSAGE AND ADMINISTRATION” sections of Aggrenox<sup>®</sup> labeling, that, ***“Aggrenox<sup>®</sup> is not interchangeable with the individual components of aspirin and Persantine<sup>®</sup> (immediate-release dipyridamole) Tablets”*** for secondary stroke prevention in patients with a previous stroke or TIA.

### *3.1.c £European Stroke Prevention Study 2 – efficacy findings<sup>3</sup>*

Aggrenox<sup>®</sup> was studied in a multicenter, randomized, double-blind, parallel-group, placebo-controlled, two-by-two factorial design, 2-year study conducted in 6,602 subjects greater than 18 years of age. Details of the study are presented in Table 2. Eligible subjects had a qualifying cerebrovascular event [TIA (24%) or stroke (76%)] within three months preceding inclusion in the study. Subjects were randomized into one of four treatment groups: extended-release dipyridamole 200 mg and immediate-release aspirin 25 mg [Aggrenox<sup>®</sup>] (n=1650), extended-release dipyridamole 200 mg alone (n=1654), immediate-release aspirin 25 mg alone (n=1649), or placebo (n=1649) administered twice daily (morning and evening). Fifty-eight percent of the subjects were male and 42% were female; the mean age was 66.7 years. No significant differences existed between treatment groups for gender, age, height, weight, geographic region, and qualifying cerebrovascular event. The study protocol defined two primary efficacy parameters: stroke (fatal or non-fatal) and death from all causes. Additionally, four secondary efficacy endpoints (MI; other vascular events including pulmonary embolism, deep vein thrombosis, peripheral arterial occlusion or retinal vascular accident; TIAs; and ischemic events including MI, stroke and sudden death of thrombotic origin) were evaluated. Study subjects were evaluated prior to study randomization and followed every three months for the two-year duration of the study.

According to the package insert and data on file, the incidence of fatal and non-fatal stroke over the two-year study period was 9.5% (Aggrenox<sup>®</sup>), 12.5% (aspirin), 12.8% (extended-release dipyridamole), and 15.2% (placebo). Pairwise treatment group comparisons of ESPS-2 data demonstrated that fatal and non-fatal stroke risk was reduced by 16.5% ( $p=0.036$ ) with extended-release dipyridamole 200 mg alone and 18.9% ( $p=0.009$ ) with immediate-release aspirin 25 mg alone vs. placebo (package insert; data on file). The combination of extended-release dipyridamole 200 mg and immediate-release aspirin 25 mg (Aggrenox<sup>®</sup>) reduced the risk of fatal and non-fatal stroke by 36.8% ( $p<0.001$ ) compared with placebo, supporting the additive antiplatelet efficacy of the active ingredients (package insert; data on file). Aggrenox<sup>®</sup> therapy reduced the risk of fatal and non-fatal stroke by 22.1% ( $p<0.008$ ) compared with aspirin and

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<sup>3</sup> Data from this trial was published (Diener et al., 1996) and is presented in Table 2. However, additional analyses were conducted prior to unblinding for the New Drug Application. Results of these analyses, including the combined endpoint of stroke (fatal and non-fatal), MI (fatal and non-fatal), and vascular death are presented here and in Table 2.

24.4% ( $p=0.002$ ) compared with extended-release dipyridamole 200 mg alone (package insert; data on file). Clinically significant reductions in the risk of stroke and death (all cause mortality) were also demonstrated in patients treated with extended-release dipyridamole (15.6%,  $p=0.013$ ), immediate-release aspirin 25 mg alone (13.8%,  $p=0.01$ ), and Aggrenox<sup>®</sup> (24.2%,  $p<0.001$ ) vs. placebo (package insert; data on file). Aggrenox<sup>®</sup> therapy reduced the risk of stroke and death (all cause mortality) by 12.1% ( $p=0.084$ ) compared with immediate-release aspirin 25 mg alone and 10.3% ( $p=0.079$ ) compared with extended-release dipyridamole 200 mg alone (package insert; data on file). However, none of the treatments significantly reduced the risk of death (due to all causes) alone.

Analyses of ESPS-2 data for secondary efficacy parameters showed that Aggrenox<sup>®</sup> therapy significantly reduced the risk of other vascular events, TIAs and ischemic events vs. extended-release dipyridamole 200 mg alone, immediate-release aspirin 25 mg alone and placebo ( $p<0.001$ ). While slightly fewer patients suffered MIs in the Aggrenox<sup>®</sup> treatment group ( $n=35$ , 2.1%), the risk reduction for MI was not statistically significant versus extended-release dipyridamole alone ( $n=48$ , 2.9%), immediate-release aspirin 25 mg alone ( $n=39$ , 2.4%), or placebo ( $n=45$ , 2.7%) (package insert; data on file). The small number of MIs allowed only a low-powered comparison, leading to a broad 95% confidence interval. In addition to the impact on MIs, Aggrenox<sup>®</sup> was shown to significantly ( $p<0.01$ ) reduce the incidence of TIAs vs. placebo (10.5% Aggrenox vs. 16.5% placebo) (package insert; data on file). This reduction in incidence translated into a relative risk reduction of 35.9% ( $p<0.001$  vs. placebo). Risk reductions for other vascular events (combined endpoint of lung embolism, deep venous thrombosis, obstruction of peripheral arteries, retinal artery occlusion) and ischemic events (combined endpoint of fatal or non-fatal stroke/MI/death) were also significant ( $p<0.001$ ) at 61.6% (other vascular events) and 32.8% (ischemic events) for Aggrenox<sup>®</sup> vs. placebo (package insert; data on file). Vascular death, a composite endpoint that includes deaths due to stroke, myocardial infarction, other vascular events, or cardiac failure, as well as sudden deaths, hemorrhagic deaths (non-cerebral fatal bleeding), and deaths of unknown cause, was not identified as a secondary endpoint in the trial protocol, but was added to the analysis plan during blinded data review to facilitate comparison of the ESPS-2 results with those from other stroke prevention studies. While slightly fewer patients died due to a vascular event in the AGGRENOX treatment group ( $n=117$ , 7.1%), the risk reduction for vascular death was not statistically significant versus extended release dipyridamole alone ( $n=125$ , 7.6%), immediate release aspirin 25 mg alone ( $n=118$ , 7.2%), or placebo ( $n=124$ , 7.5%).

### 3.1.d *Safety of Aggrenox<sup>®</sup>*<sup>4</sup>

Both dipyridamole and aspirin have been available and widely used in the US for over thirty years and one-hundred years, respectively, and have well established clinical safety profiles. Adverse events (AE) expected to occur during therapy with Aggrenox<sup>®</sup> are those AEs already known to occur with its components, dipyridamole and aspirin.

ESPS-2 confirmed the safety of dipyridamole and aspirin alone and in combination in the prevention of fatal and non-fatal stroke in patients who had transient ischemia of the brain or

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<sup>4</sup> Data from this trial was published (Diener et al. 1996, 2001) and is presented in Table 3. However, additional analyses were conducted prior to unblinding for the New Drug Application. Results of these analyses are presented here and in Table 3.

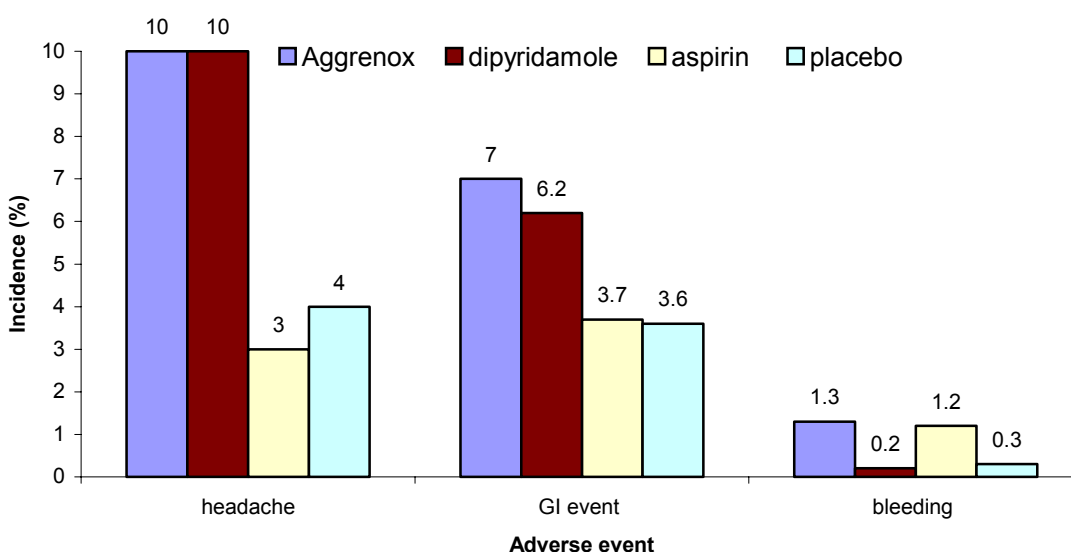
ischemic stroke (Diener et al., 1996; data on file). All 6,602 patients in ESPS-2 were evaluated for safety at one month, three months and every three months thereafter for the two-year duration of the study. Safety evaluations consisted of AE monitoring, laboratory examinations and blood pressure measurements.

Ten AEs were found to have a  $\geq 1\%$  incidence in the Aggrenox<sup>®</sup> treatment group compared with the placebo treatment group (Diener et al., 2001; data on file). Headache, nausea and vomiting were reported in a similar number of patients treated with Aggrenox<sup>®</sup> and extended-release dipyridamole 200 mg alone, while dyspepsia, hemorrhage, melena and anemia had a similar incidence in the Aggrenox<sup>®</sup> and immediate-release aspirin 25 mg alone treatment groups. These findings suggest that increased incidence of headache, nausea and vomiting were related to the dipyridamole component while increased incidence of dyspepsia, hemorrhage, melena and anemia were related to the aspirin component, consistent with known AE profiles of these agents. Purpura occurred more than twice as often in the Aggrenox<sup>®</sup> treatment group compared to either the extended-release dipyridamole 200 mg alone or the immediate-release aspirin 25 mg alone treatment groups, and more than three times as often in the placebo treatment group. These findings are consistent with evidence that suggests both dipyridamole and aspirin independently contribute to the development of this AE. Incidence of the most commonly reported AEs with Aggrenox<sup>®</sup> therapy declined notably during the first six months of the ESPS-2 study, with no new types of AEs reported over the remainder of the 24-month study course.

Although incidence of bleeding events was low throughout the 24-month course of the ESPS-2 study, incidence of gastrointestinal bleeding (including rectal hemorrhage, melena, hematemesis, hemorrhagic ulceration and bloody diarrhea) and intracranial hemorrhage (including cerebral and subarachnoid hemorrhage) was greater in the Aggrenox<sup>®</sup> treatment group (4.1% and 0.6% respectively) compared to extended-release dipyridamole 200 mg alone (2.2% and 0.5%), immediate-release aspirin 25 mg alone (3.2% and 0.4%) or placebo (2.1% and 0.4%) (package insert; data on file). Similar to observations with more common side effects, the incidence of bleeding events was greatest during the first six months of the study, with no evidence of increasing numbers of bleeding events due to prolonged exposure to Aggrenox<sup>®</sup>.

Treatment cessation due to AEs was reported with equal frequency in the Aggrenox<sup>®</sup> and extended-release dipyridamole 200 mg alone treatment groups (25%), while incidence of treatment cessation was slightly less in the immediate-release aspirin 25 mg alone (19%) and placebo (21%) treatment groups (Diener et al., 1996). The AEs most commonly associated with treatment cessation in the Aggrenox<sup>®</sup> treatment group were headache and gastrointestinal disorders (especially nausea). Figure 2 depicts the incidence of AE-related discontinuation (Diener et al., 1996).

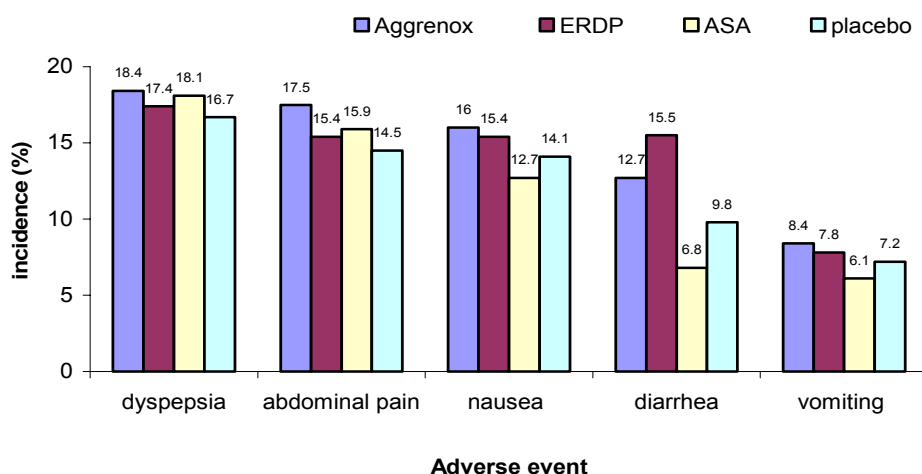
**Figure 2. Incidence (%) of AE-related discontinuation (ESPS-2)**



$p < 0.001$  for overall comparison between treatment groups for each AE; Source: Diener et al., 1996

Figure 5 depicts the incidence of GI-related AEs. Note that these events occur with a similar incidence across all treatment groups. This phenomenon is expected, given the safety profiles of the individual components of Aggrenox<sup>®</sup>. Both extended-release dipyridamole and aspirin have documented GI side effects; these effects are seen with Aggrenox<sup>®</sup> at a slightly, but not clinically significantly, higher incidence.

**Figure 3. Incidence (%) of GI AEs in ESPS-2 across all treatment groups**



Cardiac safety was also explored (Diener et al., 2001; data on file). Analyses of ESPS-2 data revealed that the proportion of patients enrolled with a past medical history of ischemic heart disease (IHD) or myocardial infarction (MI) were well-balanced between the four treatment

groups, constituting 35.1% and 13.5% of the total enrollment respectively. Evaluation of reported adverse cardiac effects (angina pectoris and MI) identified no cardiac risk attributable to the use of Aggrenox<sup>®</sup> in patients with a past medical history of IHD or MI with stable symptomatology. Episodes of new angina pectoris or deterioration of pre-existing angina pectoris (n=553) were reported by 8.4% of subjects enrolled in the trial; the incidence of these events was similar across all active treatment groups. New MI (n=167) was reported by 2.5% of subjects enrolled in ESPS-2, with Aggrenox<sup>®</sup> showing a trend towards a reduced rate of MI. Additionally, analyses of mortality data demonstrated no evidence of adverse cardiac effects associated with Aggrenox<sup>®</sup> therapy that suggests a mortality risk.

### **3.2 Tabular summaries of clinical efficacy and safety**

Table 2 summarizes the efficacy of Aggrenox<sup>®</sup> in ESPS-2. Table 3 summarizes the safety associated with Aggrenox<sup>®</sup>, based on ESPS-2. Please note that there are slight differences (non-significant) in the efficacy and safety data between the publication and package insert/data on file. These differences are due to the different data handling rules for the new drug application (NDA), clinical trial report (CTR), and the subsequent publication (Diener et al. 1996).

The following abbreviations are used in all tables throughout the document:

AEs	adverse events
AGG	Aggrenox
ASA	acetylsalicylic acid (aspirin)
ERDP	extended-release dipyridamole
MI	myocardial infarction
PVX	Plavix
RIND	reversible ischemic neurologic deficit
TIA	transient ischemic attack
TTP	thrombotic thrombocytopenic purpura

**Table 2. Efficacy of Aggrenox® in ESPS 2**

Study Design	Study Sample and Criteria	Endpoints/Results
<i>Diener et al., 1996; package insert for Aggrenox and data on file</i>		
<p><b>Objective</b></p> <ul style="list-style-type: none"> <li>To determine the efficacy of 4 prevention strategies for secondary stroke in patients who had suffered prior ischemic stroke or TIA</li> </ul> <p><b>Setting</b></p> <ul style="list-style-type: none"> <li>Multicenter</li> <li>Conducted in Europe</li> </ul> <p><b>Design</b></p> <ul style="list-style-type: none"> <li>Randomized, double-blind, placebo-controlled</li> <li>Phase III</li> </ul> <p><b>Drug administration</b></p> <ul style="list-style-type: none"> <li>AGG (ASA 25 mg/ERDP 200 mg) BID</li> <li>ASA 25 mg BID</li> <li>ERDP 200 mg BID</li> <li>placebo BID</li> </ul> <p><b>Study period</b></p> <ul style="list-style-type: none"> <li>2 years</li> </ul>	<p><b>Study sample</b></p> <ul style="list-style-type: none"> <li>N=6602</li> <li>N=1650 (AGG)</li> <li>N=1649 (ASA)</li> <li>N=1654 (ERDP)</li> <li>N=1649 (placebo)</li> <li>42% female</li> <li>66.7 years (mean age)</li> </ul> <p><b>Inclusion criteria</b></p> <ul style="list-style-type: none"> <li>&gt; 18 years of age</li> <li>TIA or completed ischemic stroke within prior 3 months</li> </ul> <p><b>Exclusion criteria</b></p> <ul style="list-style-type: none"> <li>Recent history of peptic ulcer, other gastrointestinal bleeding or other bleeding disturbance, hypersensitivity or intolerance to study medication, any condition requiring continued use of ASA or anti-coagulants</li> </ul>	<p><b>Primary efficacy</b></p> <p>Primary efficacy endpoints defined as stroke (fatal or non-fatal), death (all cause mortality), or stroke (fatal or non-fatal) and/or death (all cause mortality)</p> <p><i>Based on publication</i></p> <ul style="list-style-type: none"> <li>2-year fatal or non-fatal stroke rate: 9.9% (AGG), 12.9% (ASA), 13.2% (ERDP), 15.8% (placebo)</li> <li>Risk reduction of fatal or non-fatal stroke vs. placebo: 37.0% (AGG) (<math>p&lt;0.001</math>), 18.1% (ASA) (<math>p=0.013</math>), 16.3% (ERDP) (<math>p=0.039</math>)</li> <li>Risk reduction of fatal or non-fatal stroke or death vs. placebo: 24.4% (AGG) (<math>p&lt;0.001</math>), 13.2% (ASA) (<math>p=0.016</math>), 15.4% (ERDP) (<math>p=0.015</math>)</li> <li>Risk reduction of fatal or non-fatal stroke for AGG vs. monotherapy: 23.1% (vs. ASA) (<math>p=0.006</math>), 24.7% (vs. ERDP) (<math>p=0.002</math>)</li> <li>Risk reduction of fatal or non-fatal stroke or death (all cause) vs. monotherapy: 12.9% (vs. ASA), 10.7% (vs. ERDP)</li> <li>No treatment significantly reduced risk of death (all cause) alone</li> <li>Predictors of fatal or non-fatal stroke (based on Cox model): cerebrovascular event (<math>c=1.62</math>), alcohol consumption (<math>c=1.51</math>), smoking (<math>c=1.22</math>), diabetes (<math>c=1.40</math>), MI (<math>c=1.27</math>)</li> </ul> <p><i>Based on package insert and data on file</i></p> <ul style="list-style-type: none"> <li>2-year fatal or non-fatal stroke rate: 9.5% (AGG), 12.5% (ASA), 12.8% (ERDP), 15.2% (placebo)</li> <li>Risk reduction of fatal or non-fatal stroke vs. placebo: 36.8% (AGG) (<math>p&lt;0.001</math>), 18.9% (ASA) (<math>p=0.009</math>), 16.5% (ERDP) (<math>p=0.036</math>)</li> <li>Risk reduction of fatal or non-fatal stroke or death (all cause) vs. placebo: 24.2% (AGG) (<math>p&lt;0.001</math>), 13.8% (ASA) (<math>p=0.01</math>), 15.6% (ERDP) (<math>p=0.013</math>)</li> <li>Risk reduction of fatal or non-fatal stroke for AGG vs. monotherapy: 22.1% (vs. ASA) (<math>p&lt;0.008</math>), 24.4% (vs. ERDP) (<math>p=0.002</math>)</li> <li>Risk reduction of fatal or non-fatal stroke or death (all cause) vs. monotherapy: 12.1% (vs. ASA) (<math>p=0.084</math>), 10.3% (vs. ERDP) (<math>p=0.079</math>)</li> </ul> <p><b>Secondary efficacy</b></p> <p>Secondary efficacy endpoints defined as TIA, MI, other vascular events (combined endpoint of lung embolism, deep venous thrombosis, obstruction of peripheral arteries, retinal artery occlusion), and ischemic events (combined endpoint of fatal or non-fatal stroke/MI/death)</p> <p><i>Based on publication</i></p> <ul style="list-style-type: none"> <li>Incidence of TIA: 10.6% (AGG), 12.6% (ASA), 13.2% (ERDP), 16.5% (placebo) (<math>p&lt;0.01</math> AGG vs. placebo)</li> <li>Risk reduction of TIA vs. placebo: 35.9% (AGG) (<math>p&lt;0.001</math>), 21.9% (ASA) (<math>p&lt;0.01</math>), 18.3% (ERDP) (<math>p&lt;0.01</math>)</li> <li>Risk reduction of MI: not significant with monotherapy of either drug or AGG</li> <li>Incidence of other vascular events: 1.3% (AGG), 2.3% (ASA), 2.1% (ERDP), 3.3% (placebo)</li> <li>Incidence of ischemic events: 12.5% (AGG), 16.1% (ASA), 16.4% (ERDP), 18.6% (placebo)</li> </ul> <p><i>Based on package insert and data on file</i></p> <ul style="list-style-type: none"> <li>Risk reduction of OVE vs. placebo: 61.6% (AGG) (<math>p&lt;0.001</math>)</li> <li>Incidence of ischemic events: 12.5% (AGG), 16.1% (ASA), 16.4% (ERDP), 18.6% (placebo)</li> <li>Risk reduction of ischemic events vs. placebo: 32.8% (AGG) (<math>p&lt;0.001</math>)</li> </ul>

**Table 3. Safety of Aggrenox®**

Citation	Safety Findings
<p><i>Diener et al., 1996, 2001; package insert for Aggrenox; data on file.</i></p>	<p><b><u>Treatment patterns</u></b></p> <ul style="list-style-type: none"> <li>• 1650 subjects treated with AGG</li> <li>• 1654 subjects treated with ERDP alone</li> <li>• 1649 subjects treated with ASA alone</li> <li>• 1649 subjects treated with placebo</li> </ul> <p><b><u>Overall safety</u></b> (based on Aggrenox package insert)</p> <ul style="list-style-type: none"> <li>• Most commonly reported AEs → headache, GI event (nausea, vomiting, dyspepsia, bleeding, gastric pain, diarrhea)</li> <li>• Headache (<math>p&lt;0.001</math>) and GI events (<math>p=0.042</math>) most frequently reported AEs by patients treated with active drug (AGG, ERDP, ASA) vs. placebo <ul style="list-style-type: none"> <li>• Headache → 39.2% (AGG), 38.3% (ERDP), 33.8% (ASA), 32.9% (placebo)</li> <li>• Dyspepsia → 18.4% (AGG), 17.4% (ERDP), 18.1% (ASA), 16.7% (placebo)</li> <li>• Abdominal pain → 17.5% (AGG), 15.4% (ERDP), 15.9% (ASA), 14.5% (placebo)</li> <li>• Nausea → 16.0% (AGG), 15.4% (ERDP), 12.7% (ASA), 14.1% (placebo)</li> <li>• Diarrhea → 12.7% (AGG), 15.5% (ERDP), 6.8% (ASA), 9.8% (placebo)</li> <li>• Vomiting → 8.4% (AGG), 7.8% (ERDP), 6.1% (ASA), 7.2% (placebo)</li> <li>• Hemorrhaging → 3.2% (AGG), 1.5% (ERDP), 2.8% (ASA), 1.5% (placebo)</li> <li>• Purpura → 1.4% (AGG), 0.5% (ERDP), 0.5% (ASA), 0.4% (placebo)</li> <li>• Anemia → 1.6% (AGG), 1.0% (ERDP), 1.2% (ASA), 0.5% (placebo)</li> </ul> </li> </ul> <p><b><u>Cardiac safety</u></b> (based on Diener et al., 2001; data on file)</p> <ul style="list-style-type: none"> <li>• New episodes of angina pectoris or deterioration of pre-existing angina → 9.1% (AGG), 8.4% (ERDP), 7.5% (ASA), 8.5% (placebo)</li> <li>• New MIs → 2.1% (AGG), 2.9% (ERDP), 2.4% (ASA), 2.7% (placebo)</li> </ul> <p><b><u>Discontinuation</u></b></p> <p><i>Based on Diener et al., 1996</i></p> <ul style="list-style-type: none"> <li>• Discontinuation due to AEs (overall) → 15.9% (AGG), 8.6% (ASA), 15.1% (ERDP), 7.7% (placebo) (<math>p&lt;0.001</math> for overall comparison)</li> <li>• Discontinuation due to AEs (specific): <ul style="list-style-type: none"> <li>• Headache → 8.1% (AGG), 1.9% (ASA), 7.9% (ERDP), 2.4% (placebo) (<math>p&lt;0.001</math> for overall comparison)</li> <li>• GI event → 7.0% (AGG), 3.7% (ASA), 6.2% (ERDP), 3.6% (placebo) (<math>p&lt;0.001</math> for overall comparison)</li> <li>• Bleeding events → 1.3% (AGG), 1.2% (ASA), 0.2% (ERDP), 0.3% (placebo) (<math>p&lt;0.001</math> for overall comparison)</li> </ul> </li> </ul> <p><i>Based on Aggrenox package insert</i></p> <ul style="list-style-type: none"> <li>• Discontinuation due to AEs (overall) → 25% (AGG), 25% (ERDP), 19% (ASA), 21% (placebo) (<math>p&lt;0.001</math> for overall comparison)</li> <li>• Discontinuation due to AEs (specific): <ul style="list-style-type: none"> <li>• Headache → 10% (AGG), 10% (ERDP), 3% (ASA), 4% (placebo)</li> <li>• Dizziness → 5% (AGG), 6% (ERDP), 4% (ASA), 4% (placebo)</li> <li>• Nausea → 6% (AGG), 6% (ERDP), 3% (ASA), 3% (placebo)</li> <li>• Abdominal pain → 4% (AGG), 4% (ERDP), 3% (ASA), 3% (placebo)</li> <li>• Dyspepsia → 6% (AGG), 6% (ERDP), 3% (ASA), 3% (placebo)</li> <li>• Vomiting → 3% (AGG), 3% (ERDP), 2% (ASA), 1% (placebo)</li> <li>• Diarrhea → 2% (AGG), 2% (ERDP), &lt;1% (ASA), &lt;1% (placebo)</li> </ul> </li> </ul> <p><b><u>Compliance</u></b> (based on Diener et al., 1996)</p> <ul style="list-style-type: none"> <li>• Used plasma assays of ASA and ERDP → 84% ASA patients vs. 97% ERDP patients (may be lower in ASA patients due to poor detection by assay)</li> </ul>

### 3.3 Health economic support of Aggrenox<sup>®</sup>

A health economic analysis was conducted to determine the cost-effectiveness of Aggrenox<sup>®</sup> vs. aspirin monotherapy and Plavix<sup>®</sup> vs. aspirin monotherapy for the prevention of recurrent ischemic stroke. Details of this analysis are presented in Table 4 (Shah & Gondek, 2000). Efficacy data were retrieved from two large-scale European trials, ESPS-2 and CAPRIE, in which patients were followed for 2 years to determine the incidence of recurrent stroke or death. Patients enrolled in ESPS-2 (n=6602) had suffered a transient ischemic attack (TIA) or a completed ischemic stroke; details of the clinical aspects of this trial were previously presented in Table 2. Data used for the economic analysis for ESPS-2 were retrieved only from the published efficacy data (Diener et al., 1996). A subgroup of patients in CAPRIE (n=6431) entered the trial with a completed ischemic stroke as a qualifying event. Cost estimates for resource utilization associated with stroke were obtained from a published Medicare claims analysis. Obtained costs, adjusted to 1999 US \$, represented acute-care hospitalizations, rehabilitation hospitalizations, physician services, hospital outpatient, home health, skilled nursing facility, and nursing home and durable medical equipment. Costs of outpatient drug expenditures were based on the average wholesale price.

Development of the model rested on the following assumptions:

- Costs for hospitalization after the initial stroke are not included
- All patients are hospitalized after a recurrent ischemic stroke
- Each patient in the cohort can have a maximum of one recurrent ischemic stroke during the two-year evaluation period
- Recurrent ischemic stroke rates are accounted for on a quarterly basis and occur at equal rates each quarter
- Deaths are accounted for at the midpoint of the analysis
- Patients are 100% compliant with their drug therapy
- The cost of adverse events associated with drug therapy are not included
- Withdrawal rates and switch rates associated with failed therapy are equal for all treatments

Cost-effectiveness was measured as cost per stroke averted, as antiplatelet therapy leads to a reduction in the relative risk of recurrent strokes. Sensitivity analyses were conducted to test five parameters: 1) change in the cost of stroke of  $\pm 20\%$ ; 2) change in the baseline risk of recurrent stroke of  $\pm 20\%$ ; 3) change in the relative risk reduction of Aggrenox<sup>®</sup> vs. aspirin of  $\pm 10\%$ ; 4) change in the relative risk reduction of aspirin vs. placebo of  $\pm 10\%$ ; and 5) change in the relative risk reduction of Plavix<sup>®</sup> vs. aspirin of  $\pm 10\%$ . Additional analyses were conducted to determine the incremental cost and cost-effectiveness of Aggrenox<sup>®</sup> vs. aspirin and Plavix<sup>®</sup> vs. aspirin during first and second years after the primary stroke.

Results suggest that treatment with Aggrenox<sup>®</sup>, compared with aspirin monotherapy, prevents the occurrence of an additional 33 recurrent strokes per 1000 patients. Incremental cost per stroke averted is \$28,472. Plavix<sup>®</sup> prevents an additional 11 recurrent strokes, compared with aspirin monotherapy, at an incremental cost per stroke averted of \$161,316. Across each

sensitivity analysis, Aggrenox<sup>®</sup> remained relatively cost-effective with incremental cost per stroke averted ranging from \$20,216 (increase baseline risk of recurrent stroke by 20%) to \$40,854 (decrease baseline risk of recurrent stroke by 20%). Results for Plavix<sup>®</sup> ranged from \$129,687 (increase baseline risk of recurrent stroke by 20%) to \$208,819 (decrease baseline risk of recurrent stroke by 20%). Additional analyses showed that Aggrenox<sup>®</sup> was cost-effective compared with aspirin monotherapy during the first and second years of therapy. Costs per case averted were \$25,242 (year 1) and \$40,170 (year 2). Plavix<sup>®</sup> was not cost-effective compared with aspirin monotherapy, as demonstrated by costs per case averted of \$105,559 (year 1) and \$201,923 (year 2).

**Table 4. Summary of Pharmacoeconomic Studies with Aggrenox<sup>®</sup>**

Background	Service Use/Unit Costs	Results
<i>Shah &amp; Gondek, 2000</i> <i>(efficacy data based on Diener et al., 1996 and presented in Table 2)</i>		
<b>Objective</b> <ul style="list-style-type: none"> <li>To determine cost-effectiveness of AGG vs. ASA and PVX vs. ASA in secondary stroke prevention for patients suffering a prior completed ischemic stroke or TIA</li> </ul> <b>Study design</b> <ul style="list-style-type: none"> <li>Spreadsheet model based on clinical trial data</li> <li>Cost-effectiveness analysis</li> <li>3<sup>rd</sup>-party payer</li> </ul> <b>Outcome measure</b> <ul style="list-style-type: none"> <li>Cost per stroke averted</li> </ul>	All costs adjusted to 1999 US \$  <u>Resource utilization costs</u> <ul style="list-style-type: none"> <li>acute-care hospitalizations</li> <li>rehabilitation hospitalizations</li> <li>physician services</li> <li>durable medical equipment</li> <li>hospital outpatient</li> <li>home health</li> <li>skilled nursing facility</li> <li>nursing home</li> </ul> <u>Drug costs</u> <ul style="list-style-type: none"> <li>average wholesale price</li> </ul>	<b>Base-case analysis</b> <ul style="list-style-type: none"> <li>Prevention of recurrent strokes per 1000: 33 strokes prevented (AGG vs. ASA) vs. 11 strokes prevented (PVX vs. ASA)</li> <li>Cost per stroke averted: \$28,472 (AGG vs. ASA) vs. \$161,316 (PVX vs. ASA)</li> </ul> <u>Sensitivity analysis (cost per stroke averted)</u> <ul style="list-style-type: none"> <li>Cost of stroke ↑ 20%: \$24,110 (AGG vs. ASA) vs. \$155,749 (PVX vs. ASA)</li> <li>Cost of stroke ↓ 20%: \$32,835 (AGG vs. ASA) vs. \$166,884 (PVX vs. ASA)</li> <li>Baseline risk ↑ 20%: \$20,216 (AGG vs. ASA) vs. \$129,687 (PVX vs. ASA)</li> <li>Baseline risk ↓ 20%: \$40,854 (AGG vs. ASA) vs. \$208,819 (PVX vs. ASA)</li> <li>Relative risk reduction of ASA vs. placebo ↑ 10%: \$29,335 (AGG) vs. \$164,693 (PVX)</li> <li>Relative risk reduction of ASA vs. placebo ↓ 10%: \$27,640 (AGG) vs. \$158,057 (PVX)</li> <li>Relative risk reduction ↑ 10%: \$23,901 (AGG vs. ASA) vs. \$144,121 (PVX vs. ASA)</li> <li>Relative risk reduction vs. ASA ↓ 10%: \$34,060 (AGG vs. ASA) vs. \$182,333 (PVX vs. ASA)</li> <li>Cost per stroke averted in first year: \$25,242 (AGG vs. ASA) vs. \$105,559 (PVX vs. ASA)</li> <li>Cost per stroke averted in second year: \$40,170 (AGG vs. ASA) vs. \$201,923 (PVX vs. ASA)</li> </ul> <b>Conclusions</b> <ul style="list-style-type: none"> <li>AGG is cost-effective compared with ASA monotherapy</li> <li>PVX is not cost-effective compared with ASA monotherapy</li> </ul>

Another analysis was conducted that used a Markov model to measure the clinical benefits and economic consequences of three different prevention strategies: 1) aspirin, 325 mg daily; 2) aspirin 50 mg/day and dipyridamole 400 mg/day (the traditional dosage for Aggrenox<sup>®</sup>, although the authors do not specify if patients were treated with Aggrenox<sup>®</sup> or the individual, generic components); 3) clopidogrel bisulfate, 75 mg/day (again, the authors do not specify if branded Plavix<sup>®</sup> was used) (Sarasin et al., 2000). Results confirmed that combination therapy of aspirin

and dipyridamole was more effective (based on quality-adjusted life-years, QALY) and less costly than aspirin monotherapy, whereas clopidogrel bisulfate was more effective *and* more costly than aspirin monotherapy.

However, several limitations of this article prevent its widespread use as support for addition of Aggrenox<sup>®</sup> to a managed care formulary in the US. Parameters and findings from this analysis are compared with that conducted by Shah and Gondek (2000) in Table 5. Given these limitations, the article by Sarasin et al. (2000) is not discussed in detail in this document.

**Table 5. Comparison of economic publications for Aggrenox<sup>®</sup>**

Parameter	Sarasin et al., 2000	Shah and Gondek, 2000
<b>Drug analyzed</b>	No specific mention of Aggrenox <sup>®</sup> ; authors may be referring to generic extended-release dipyridamole (not available in the US) and aspirin.	Specific use of Aggrenox <sup>®</sup>
<b>Drug cost per day</b>		
Aspirin	\$0.02	\$0.06
Aspirin + Dipyridamole	\$0.60	\$2.95
Clopidogrel	\$2.40	\$3.01
	(based on European drug costs)	(based on average wholesale prices – more relevant for managed care organization)
<b>Model software</b>	Computer simulation Markov model	Excel spreadsheet model
<b>Cost-effectiveness measure</b>	<ul style="list-style-type: none"> <li>• Cost per QALY</li> <li>• Lifetime cost effectiveness model</li> </ul>	<ul style="list-style-type: none"> <li>• Cost per stroke averted</li> <li>• 2-year cost effectiveness model (more relevant for managed care organization)</li> </ul>
<b>Perspective</b>	Societal perspective	Payer perspective (more relevant for managed care organization)
<b>Endpoint(s)</b>	Stroke, MI, Death	Stroke, Death
<b>Factors included in the model</b>	<ul style="list-style-type: none"> <li>• Costs of AEs and initial hospitalization included</li> <li>• Nursing home costs not included</li> </ul>	<ul style="list-style-type: none"> <li>• Costs of AEs and initial hospitalization not included</li> <li>• Nursing home costs included</li> </ul>

#### **4 BUDGET IMPACT**

A formal budget impact analysis has not been completed; hence, cost-effectiveness data is presented here.

In a cost-effectiveness analysis, Aggrenox<sup>®</sup> was shown to be more cost-effective than aspirin for the prevention of recurrent ischemic stroke. Compared with aspirin, treatment with Aggrenox<sup>®</sup> prevented the occurrence of an additional 33 recurrent strokes per 1000 patients. The incremental cost per stroke averted was calculated to be \$28,472. Plavix<sup>®</sup>, currently the standard of care in the prevention of recurrent ischemic stroke, prevented an additional 11 recurrent strokes vs. aspirin. The incremental cost per stroke averted was \$161,316. Indeed, Aggrenox<sup>®</sup> is more-cost effective than aspirin, making the drug a better option compared with aspirin. Please see additional cost-effectiveness data presented in Section 3.3, “Health economic support for Aggrenox<sup>®</sup>,” for further information.

## **5.1.1 CLINICAL VALUE AND OVERALL COST**

This section demonstrates the overall value that Aggrenox<sup>®</sup> may provide as prevention in secondary stroke.

### **5.1 Clinical efficacy of Aggrenox<sup>®</sup>**

Patients recovering from a first stroke or a TIA are at high risk for stroke recurrence and related morbidity/mortality, a fact confirmed by two independent studies. Vickrey et al. (2001) used managed care claims data to estimate the occurrence of secondary ischemic events (e.g., stroke, MI, and vascular death) in patients who had suffered from peripheral arterial disease, a prior stroke, or prior acute MI. Results suggest that >75% of secondary events in the stroke cohort were stroke (Vickrey et al., 2001). This finding clearly suggests that patients suffering a primary stroke are at great risk for a secondary stroke. Johnston et al. (2000) studied a patient cohort selected from 16 hospitals in a health maintenance organization. Patients suffering from an initial TIA were also shown to be at greater risk for suffering a stroke: 10.5% of patients who suffered a TIA presented with a stroke within 90 days of the index event (Johnston et al., 2000). Over 50% of these strokes occurred within the first two days following the TIA. This data confirms that the short-term risk of stroke following a TIA is substantial. Both studies prove that patients suffering an initial stroke or TIA are more likely to suffer a secondary stroke compared with other ischemic events, necessitating therapy such as Aggrenox for the prevention of secondary stroke.

Substantial evidence exists that aspirin combined with extended-release dipyridamole (Aggrenox<sup>®</sup>) results in a beneficial additive effect. According to a recent meta-analysis of trials analyzing aspirin and dipyridamole monotherapy and combination therapy, combination therapy vs. placebo led to 23% reduction in the risk of nonfatal stroke and 10% reduction in the risk of all vascular events (Albers et al., 2001). Four of these trials, including ESPS-2 with Aggrenox<sup>®</sup>, included only patients who had suffered cerebrovascular accidents. Across these trials, a risk reduction of 25% was calculated for the prevention of non-fatal recurrent stroke with combination therapy vs. aspirin monotherapy. For all vascular events, a reduction of 18% for combination therapy vs. aspirin monotherapy was determined (Albers et al., 2001). Additionally, Aggrenox<sup>®</sup> has shown comparative efficacy in preventing recurrent stroke in patients with TIA or prior stroke (Albers et al., 2001)

In ESPS-2, the additive antiplatelet efficacy of the active ingredients of Aggrenox<sup>®</sup> (aspirin and extended-release dipyridamole) was shown to greatly reduce the risk of secondary stroke (findings presented are from the Aggrenox<sup>®</sup> package insert and data on file):

- Lowest incidence of fatal and non-fatal stroke in patients treated with Aggrenox<sup>®</sup> (9.5%) compared with aspirin (12.5%), extended-release dipyridamole (12.8%), and placebo (15.2%);
- Greatest reduction in risk of fatal and non-fatal stroke by Aggrenox<sup>®</sup> compared with placebo (36.8%;  $p<0.001$ ), extended-release dipyridamole (24.4%;  $p=0.002$ ), and aspirin (22.1%;  $p<0.008$ );
- Greatest reduction in risk of stroke and death (all-cause mortality) by Aggrenox<sup>®</sup> compared with placebo (24.2%;  $p<0.001$ ), extended-release dipyridamole (10.3%;  $p=0.079$ ), and aspirin (12.1%;  $p=0.084$ ).

- Reduction in risk of other vascular events, TIAs and ischemic events.

These results clearly indicate that the additive effects of aspirin and extended-release dipyridamole, administered as Aggrenox<sup>®</sup>, outweigh the benefits of either drug prescribed as monotherapy. Although each individual component has a significant effect in preventing the recurrence of stroke, the additive effects of the two agents lead to therapy that is nearly twice as effective as aspirin alone. Additionally, compliance with Aggrenox<sup>®</sup> therapy (based on plasma assays) has been shown to be >80%, a widely accepted measure of good compliance.

## **5.2 Clinical safety of Aggrenox<sup>®</sup>**

As expected, adverse events occurring during therapy with Aggrenox<sup>®</sup> were those previously known and established with the components of Aggrenox<sup>®</sup>, extended-release dipyridamole and immediate-release aspirin. In ESPS-2, headache, nausea and vomiting were reported in a similar number of patients treated with Aggrenox<sup>®</sup> and extended-release dipyridamole 200 mg alone, while dyspepsia, hemorrhage, melena and anemia had a similar incidence in the Aggrenox<sup>®</sup> and immediate-release aspirin 25 mg alone treatment groups. These findings suggest that the respective AEs were related to the individual drug components of Aggrenox<sup>®</sup>. Incidence of the most commonly reported AEs with Aggrenox<sup>®</sup>, including bleeding events, declined notably during the first six months of the ESPS-2 study, with no new types of AEs reported over the remainder of the 24-month study course. Treatment cessation due to AEs was reported with equal frequency in the Aggrenox<sup>®</sup> and extended-release dipyridamole 200 mg alone treatment groups (25%), comparable with aspirin (19%) and placebo (21%).

## **5.3 Economic value of Aggrenox<sup>®</sup>**

In an analysis comparing Aggrenox<sup>®</sup> with aspirin monotherapy, Aggrenox<sup>®</sup> was found to be more cost-effective (measured as cost per stroke averted) for the prevention of recurrent ischemic stroke. Treatment with Aggrenox<sup>®</sup>, compared with aspirin monotherapy, prevented the occurrence of an additional 33 recurrent strokes per 1000 patients, at an incremental cost per stroke averted of \$28,472. Aggrenox<sup>®</sup> remained relatively cost-effective when different parameters were varied (sensitivity analyses). Across each analysis, Aggrenox<sup>®</sup> remained relatively cost-effective compared with aspirin monotherapy. The incremental cost per stroke averted ranged from \$20,216 (increase baseline risk of recurrent stroke by 20%) to \$40,854 (decrease baseline risk of recurrent stroke by 20%). During the first and second years of therapy, Aggrenox<sup>®</sup> was cost-effective compared with aspirin monotherapy in terms of cost per case averted: \$25,242 (year 1) and \$40,170 (year 2).

In summary, several features of Aggrenox<sup>®</sup> support its addition to a managed care plan's formulary. Besides showing better efficacy than its individual ingredients of aspirin and extended-release dipyridamole, Aggrenox<sup>®</sup> exhibits a tolerable safety profile comparable to its individual components. It is also more cost-effective than aspirin monotherapy, a current option in secondary stroke prevention.

## 6 STUDY SYNOPSIS: ESPS-2

### Source

1. Data on file
2. Package Insert
3. Diener H, Cunha L, Forbes C, et al. European Stroke Prevention Study 2. Dipyridamole and acetylsalicylic acid in the secondary prevention of stroke. *J Neuro Sci* 1996;143:1-13.

### Design

- Objective – to determine efficacy of four prevention strategies for secondary stroke in patients who had suffered prior ischemic stroke or TIA
- Randomized, double-blind, placebo-controlled, multi-center trial conducted in Europe
- Drug treatments → AGG 25 mg/200 mg BID (n=1650), ASA 25 mg BID (n=1649), ERDP 200 mg BID (n=1654), placebo BID (n=1649)
- Study period – 2 years
- Primary efficacy endpoints – incidence of stroke, death, or combined stroke and death
- Secondary efficacy endpoints – incidence of TIA, MI, other vascular events, other ischemic events (discussed only in table due to space constraints)

### Study sample

- 42% female
- Mean age → 66.7 years
- Inclusion criteria → Age ≥ 18 years, TIA or completed ischemic stroke within prior 3 months
- Exclusion criteria → Recent history of peptic ulcer, other gastrointestinal bleeding or other bleeding disturbance, hypersensitivity or intolerance to study medication, any condition requiring continued use of ASA or anti-coagulants

### Results: primary efficacy

- Incidence of stroke over 2 years → 9.5% (AGG), 12.5% (ASA), 12.8% (ERDP), 15.2% (placebo)
- Risk reduction of stroke (fatal or non-fatal) vs. placebo → 36.8% (AGG) ( $p<0.001$ ), 18.9% (ASA) ( $p=0.009$ ), 16.5% (ERDP) ( $p=0.036$ )
- Risk reduction of stroke or death (all cause mortality) vs. placebo → 24.2% (AGG) ( $p<0.001$ ), 13.8% (ASA) ( $p=0.01$ ), 15.6% (ERDP) ( $p=0.013$ )
- Risk reduction of stroke (fatal or non-fatal) for AGG vs. monotherapy with ERDP or ASA → 22.1% (vs. ASA) ( $p=0.008$ ), 24.4% (vs. ERDP) ( $p=0.002$ )
- Risk reduction of stroke or death (all cause mortality) vs. monotherapy with ERDP or ASA → 12.1% (vs. ASA) ( $p=0.084$ ), 10.3% (vs. ERDP) ( $p=0.079$ )

### Safety

- Headache ( $p<0.001$ ) and GI events ( $p=0.042$ ) most frequently reported AEs by patients treated with active drug (AGG, ERDP, ASA) vs. placebo
- New episodes of angina pectoris or deterioration of pre-existing angina occurred with similar incidence rates whether subjects were treated with AGG, ERDP, ASA, or placebo.
- Trend for fewer MIs in patients treated with Aggrenox.
- Death (all cause mortality) occurred with similar incidence rates whether subjects were treated with AGG, ERDP, ASA, or placebo.
- Discontinuation due to AEs → 25% (AGG), 19% (ASA), 25% (ERDP), 21% (placebo) ( $p<0.001$  for overall comparison)

### Conclusions

- Protective effects of ASA and ERDP were additive when drugs were combined, making AGG more effective than either of its components in reducing risk associated with secondary stroke.

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